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Faculty of Medicine

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ACKNOWLEDGEMENT

On the behalf of the faculty of medicine, I would like to thank Prof. M.T. OUADA for supervising the Congress of Anaesthesia. I would like to salute the head Prof. M.E. MOEMEN and staff members of the anaesthetic department for their energetic enthusiasm to organize this first medical conference at our faculty of medicine.

Honourary President

Prof. M. ABD EL-LATIF

Dean of faculty of medicine
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SESSION I

ANAESTHESIA

AND

THE CARDIO-VASCULAR SYSTEM

Wednesday 12 December 1979

12.30 — 14.30

CHAIRMEN :

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فرع الإسكندرية : ٤٨ طريق الحرية ت ٢١١٤٣ / ٣٧٤٠٩

A STUDY OF SOME HAEMODYNAMIC EFFECTS DURING ANAESTHESIA FOR CARDIAC SURGERY

By

MOHAMED EZZAT MOEMEN

From

Department of Anaesthesia,

Zagazig Faculty of Medicine

SUMMARY :

The techniques of neuroleptanaesthesia (NLA) and combined halothane anaesthesia were compared in a total of 23 patients undergoing valve replacement or coronary artery bypass graft operations. Both techniques provided protection from the circulatory reactions of laryngoscopy and tracheal intubation. Heart rate, arterial blood pressure and rate pressure product were similar during surgery before and during the cardio-pulmonary bypass period. Blood gas tensions, pH, serum potassium and urine output did not show significant differences. Although both techniques are acceptable, halothane may be preferred on clinical basis as it ensures unconsciousness, induces a deeper and more even level of anaesthesia and provides earlier post-operative communication with the patient.

INTRODUCTION :

The limited cardiovascular reserves of the cardiac patient undergoing an open-heart surgery, necessitates meticulous anaesthetic care. Anaesthesia should induce minimal cardio-vascular depression to maintain proper flow and adequate blood pressure. Excessive sympatho-adrenal reactions which raise blood pressure

and heart rate together with inducing myocardial dysrhythmias should be avoided. Reflexes and painful and other stimuli should be controlled.

During a two-months visit to Sheffield University for training in anaesthesia for open-heart surgery, a bursary granted by the British Council, the author noticed that anaesthesia for open-heart surgery in that locality adopts one of two anaesthetic techniques ; namely :

(1) A neuroleptic technique.

(2) A combined technique including halothane.

The aim of the present study is to compare some of the haemodynamic effects of neuroleptanaesthasia and combined halothane anaesthesia during operations for open-heart.

MATERIAL and METHODS :

The study comprised 23 patients who underwent elective open-heart surgery at Northern General and Hallamshire Hospitals at Sheffield during July-August, 1979. Operations included coronary artery bypass graft and valve replacements. Other operations as correction of congenital anomalies were excluded from the study.

Pre-operative assessment of patients included the past history of heart failure, myocardial infarction and drug therapy. Evaluation also included consideration of data obtained from cardiac catheterization and lung function tests and patients showing marked depression of left ventricular performance or lung function were excluded from the study.

Pre-operative preparation :

Preparation of patients included laboratory studies for haematology, serum electrolytes, liver function, blood gas tensions and acid-base balance. Patients with apparent deviations from

normal were excluded from the study. Patients on digitalis or B-blocker therapy were ordered to discontinue the drugs 48 hours before operation.

Premedication and Monitoring :

Heart rate and arterial blood pressure were measured few times during the pre-operative day. Patients were medicated to attain a calm sleep during the night before operation. Pethidine (1 mg/kg) and/or diazepam (0.1 mg/kg) was given I.M. one hour before arrival to the anaesthetic room, where an infusion of lactated ringer solution was administered through a peripheral vein. Percutaneous insertion of a plastic cannula into left radial artery was done for measurement of arterial blood pressure by a disposable transducer. Cannulation of the right internal juglar vein was done, after anaesthesia, for monitoring the central venous pressure using a 14 cm Teflon catheter. E.C.G., lead V, heart rate and intravascular pressures were displayed on an oscilloscope with continuous tracing Oesophageal and skin temperatures were measured by electrical thermometry and during the bypass period, temperature was measured with the built-in thermometer of the oxygenator. Arterial blood gas tensions and pH were frequently measured by a radiometer. Serum potassium was measured by a flame photometer when needed. Haematocrite values were determined from arterial blood before the start of bypass and every 15 minutes during bypass. After anaesthetic induction, urinary bladder was emptied and dieuresis was measured over 3 periods ; from induction until start of bypass, during bypass and from end of bypass till end of operation.

Anaesthesia :

A group of 6 patients received neuroleptanaesthesia and a group of 17 patients received combined halothane anaesthesia.

Neuroleptanaesthesia (NLA) :

Dehydrobezperidol was I.V. injected over 3 minutes followed by fentanyl over 2 minutes. The mean doses of dehydrobenzperidol and fentanyl used for induction were 0.26 ± 0.06 mg/kg and

4.2 ± 1.1 μg/kg, respectively. Patients were receiving oxygen during induction and when they no longer responded to verbal commands and the lid reflex disappeared, pancuronium (0.1 mg/kg) facilitated cuffed endotracheal intubation. Maintenance of anaesthesia was achieved by N20 : 02, (6 : 4 L/min) using a non-rebreathing anaesthetic circuit and a Manley or Engostrom ventilator. Fentanyl was given in doses of 0.05-0.1 mg for pain relief and dehydrobenzperidol in doses of 2.5-5 mg when hypnosis seemed inadequate during the operation. At the start of the cardiopulmonary bypass 0.05 mg fentanyl and half the dose of dehydrobenzperinol were injected into the oxygenator. The mean total doses of fentanyl and dehydrobenzperidol were 13.9 ± 3.9 μg/kg and 0.58 ± 0.20 mg/kg, respectively. Additional small doses of pancuronium were given during the operation and one third the intubation dose was injected in the oxygenator at the start of the bypass. The mean total dose of pancuronium was 12.7 ± 1.9 mg and reversal was achieved by neostigmine atropine.

Combined halothane anaesthesia :

Induction was done by slow injection of 5 mg morphine sulphate followed by a sleeping dose of 2.5% of thipentone sodium, the mean induction dose being 3.1 ± 0.7 mg/kg. Patients were oxygenated during induction and pancuronium (0.1 mg/kg) was used to facilitate cuffed endotracheal intubation. Maintenance was achieved by 0.5-1.0% halothane in N_2O:O_2 (6:4 L/min.) using a non-rebreathing circuit and a Manley or Engostrom Ventilator. During the bypass period, halothane was vaporized into the oxygenator through a fluotec Mark II connected to the oxygen flow of the oxygenator. Pancuronium was given as needed before the bypass and it was injected in the oxygenator at the start of the bypass. Reversal of the relaxant effect was done by neostigmine-atropine at the end of operation and patients were extubated. The total dose of pancuronium was 13.1 ± 2.7 mg.

In both anaesthetic techniques, the lungs were inflated, during the bypass period, with 2 L/min of N_2O : O_2 (50% : 50%) with a frequency of 10 cycles/min. Ventilation was temporarily discontinued when needed by the surgeon. An end expiratory pressure of 5-10 cm H_2O was maintained during bypass. Before coming off bypass, the lungs were repeatedly exposed to pressures of 30-40 cm H_2O to re-inflate any areas of collapse.

The heart-lung machine :

It incoporates roller-pumps (American-Optical, U.S.A.), a bubble oxygenator (Shiley, U.S.A.) and a heat exchanger. Priming was done by Hartman solution with a volume of 1.5-3 litres. Sodium bicarbonate 8.4% was always added in a volume of 100 ml and Mannitol 20% in a volume of 25 ml. Haemodilution aimed at a haematocrite value of 25%. A flow of 2.4 L/m2 body surface area and hypothermia to approximately 28-30°C were used. Heparine (3 units/kg) was added before inserting the caval cannulae and its effect was neutralized after decanulation by protamine in a ratio of 2 mg protamine to every unit of heparine. The mean radial artery pressure was always kept at least 50 mmHg during bypass and microfilters were used in arterial lines. At the end of the bypass, one gm CaCl2 was given to the patient.

CO2 was vaporized in the oxygenator at the end if needed. Ventricular fibrillation was induced during the operation by topical hypothermia to produce a quiet heart. The locally prepared solution at Sheffield University has the following composition :

21 ml sterile ampoule contains :

Magnesium chloride	3.25 gm
Potassium chloride	1.19 gm
Lignocaine hydrochloride	0.073 gm

RESULTS :

Analysis of separate data from patients undergoing valve replacements or coronary artery bypass graft operations showed no significant differences in heart rate or arterial blood pressure. Premedication and catheterization produced no significant changes between the groups. So, patients of both groups were considered together.

Table (1) gives the pre-operative informations of patients. Table (2) shows the distribution of patients according to the ana-

esthetic technique. Table (3) shows the duration of intra-operative measures including, anaesthesia, surgery and bypass.

TABLE (1) :

Pre-operative data of patients.

		Valve replacement	Coronary artery graft
No.		15	8
Age	(ys)	49.4	46.7
Wt.	(kg)	71.8	76.7
Height (cm)		160.3	164.1
Surf. Area	(m2)	2.2	2.1
Mean Syst. B.P.	(mmHg)	148.3	144.2
Mean diast. B.P.	(mmHg)	89.2	85.8
Mean heart rate	(b/min)	91.5	87.2

TABLE (2) :

Distribution of Patients According to the Anaesthetic Technique

	N.L.A.	Halothane
Valve Replacement	3	12
Coronary artery graft	3	5
TOTAL	6	17

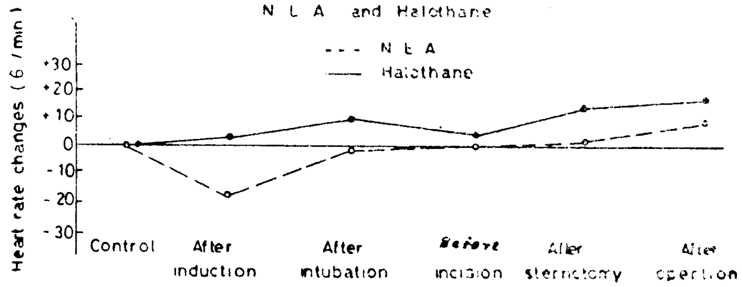
TABLE (3) :

Mean Durations ($\pm$ S.D.) of Intra-Operative Measures (minutes).

	Anaesthesia	Surgery	Bypass
N.L.A.	299 ± 51	246 ± 56	99 ± 31
Halothane	305 ± 58	270 ± 62	104 ± 40

The mean changes in heart rate, arterial blood pressure and rate-pressure product in both groups are detailed in Figs. (1, 2 and 3), respectively. Fig. (4) shows the mean changes in central venous pressure in both anaesthetic techniques. Data on bypass period are shown in Table (4). The rate of urine excretion before, during and after cardiopulmonary bypass are given in Table (5). Mean changes in PaO_2, $PaCO_2$ and pH of the blood are compared in relation to anaesthetic techniques before bypass and at the end

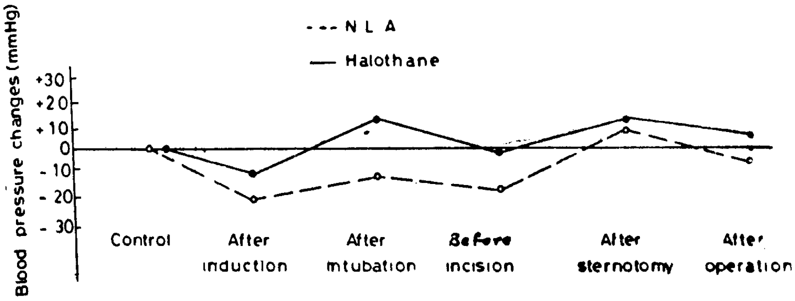
Fig (1) Mean changes in heart rate from control during N L A and Halothane



Significance of differences (> 0.05 N.S., < 0.05 = sig.)

N L A -control< 0.05	> 0.05	> 0.05	> 0.05	> 0.05
Halothane control> 0.05	> 0.05	> 0.05	> 0.05	> 0.05
N L A Halothane< 0.05	> 0.05	> 0.05	> 0.05	> 0.05

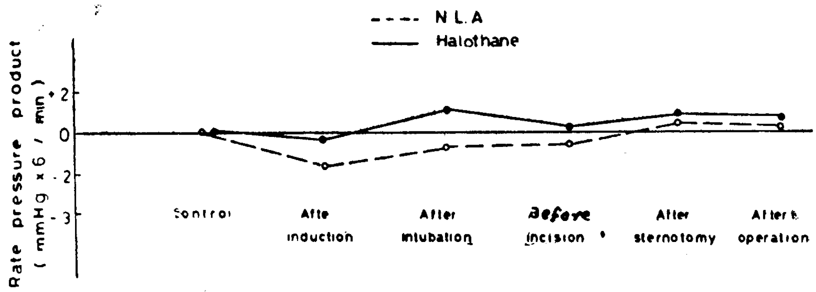
Fig. (2) Mean changes in arterial B P from control N L A and Halothane



Significance of difference (> 0.05 N.S , < 0.05 = sig.) :

N.L.A.-control	< 0.05	> 0.05	> 0.05	> 0.05	> 0.05
Halothane-control	< 0.05	> 0.05	> 0.05	> 0.05	> 0.05
N.L.A.-Halothane	> 0.05	> 0.05	> 0.05	> 0.05	> 0.05

Fig. (3) Mean changes in rate pressure product from control during N L A and halothane

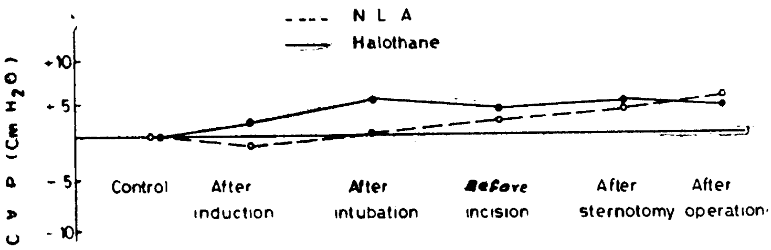


Significance of difference = (> 0.05 = N.S , < 0.05 = sig.) =

N L A -control	< 0.05	> 0.05	> 0.05	> 0.05	> 0.05
Halothane-control	> 0.05	> 0.05	> 0.05	> 0.05	> 0.05
N L A - Halothane	> 0.05	> 0.05	> 0.05	> 0.05	> 0.05

of operation and all the changes were non-significant. Details and data are included in Table (6).

Fig (4) Mean changes in C V P from control during N L.A and Halothane



Significance of difference (> 0.05 = N.S., < 0.05 = sig.)

N L A - control	> 0.05	> 0.05	> 0.05	> 0.05	> 0.05
Halothane-control	> 0.05	> 0.05	> 0.05	> 0.05	> 0.05
N L A - Halothane	> 0.05	> 0.05	> 0.05	> 0.05	> 0.05

TABLE (4) :

Data During Bypass Period.

	Mean B.P. ($\pm$S.D.) (mmHg)		Lowest Haematocrite
	Lowest	**Highest**	**(%)**
N.L.A.	47.1$\pm$11.0	81.3$\pm$19.0	24.0$\pm$2.4
Halothane	45.2$\pm$12.2	84.1$\pm$18.3	25.8$\pm$2.2
P	>0.05	>0.05	>0.05
Significance	Non	Non	Non

TABLE (5) :

Urine Excretion During N.L.A. and Halothane.

Bypass	Urine Volume (ml/h) Before	During	After
N.L.A.	34±29	160±79	148±92
Halothane	37±30	156±68	164±101
P	≥0.05	≥0.05	≥0.05
Significance	Non	Non	Non

TABLE (6) :

Blood Gas Tensions and pH Changes from Control During N.L.A. and Halothane.

		Control	Before Bypass	End of Operation
PaO2	N.L.A.	79.9 ±10.1	+40.3 ±22.6	+109.6 ±99.6
	Halothane	80.5 ±11.7	+48.2 ±27.1	+ 99.2 ±80.4
PaCO2	N.L.A.	38.7 ± 3.9	— 3.9 ± 4.9	+ 2.0 ± 5.5
	Halothane	37.9 ± 4.2	— 4.4 ± 5.0	+ 1.3 ± 6.2
pH	N.L.A.	7.41± 0.2	+ 0.05± 0.05	— 0.02± 0.06
	Halothane	7.40± 0.3	+ 0.04± 0.06	— 0.04± 0.07

DISCUSSION :

The main aim of the anaesthetic team during cardiac surgery is to protect the myocardium. The patients included in the present study had either coronary artery disease or acquired valvular lesions.. In this domain, the balance between myocardial oxygen demand and supply is critical. Myocardial oxygen demand increases with the cardiac work due to increase of both heart rate or arterial blood pressure or both (afterload) and also by increase of left ventricular filling pressure (preload). Unfortunately, there are few data available to elucidate the relationship between myocardial oxygen demand and supply as influenced by anaesthetic drugs specially in patients with myocardial disease (Tarhan et al., 1979). Recent studies have shown that nitrous oxide influences oxygen demand favourably without inducing left ventricular dysfunction (Wynne et al., 1977).

Belladona derivatives and related drugs did not constitute a part of premedication in the present study as they increase the heart rate and the incidence of arrhythmia (Eger, 1962). On the other hand, increased amounts of drugs that reduce patients apprehension were justified as apprehension may cause circulatory reactions which, in turn, increase myocardial oxygen demand (White and Tarhan, 1974 ; Tarhan et al., 1979). Diazepam was given to all patients because, in addition to its central sedative effect, it is thought to dilate the coronary and systemic vessels. It decreases left ventricular end diastolic pressures probably by reducing the afterload, preload or both. So, the intracavitory volume, myocardial wall tension and left ventricle myocardial oxygn consumption decrease (Côté et al., 1974).

Induction of anaesthesia in cardiac surgery is increasingly recognised as a critical phase of anaesthetic management.

In the present study, neuroleptanaesthesia provided good protection against heart rate and blood pressure changes during induction and intubation, in agreement with Tammisto et al. (1972) who demonstrated concomittant significant increase in plasma catecholamines. These reflex cardiovascular changes are thought to be mediated by increased sympathetic nervous activity (King et al., 1951). Neuroleptanaesthesia was shown to have a

good control of sympathetic reflexes during cardiac surgery (Maunuksela, 1977).

Thiopentone, preceded by morphine, was used for induction of anaesthesia in the halothane group. It was also able to provide protection against circulatory shifts caused by laryngoscopy and intubation. Small doses of thipentone alone used for induction of anaesthesia might induce greater heart rate and blood pressure increases during intubation (Dottori et al., 1970; Leapple and Rothlin, 1970; Lyons and Clarke, 1972; Lyons et al., 1975).

During surgery before cardiopulmonary bypass, the present study revealed that the haemodynamics, under combined halothane or neuroleptanaesthesia, were similar, in agreement with Maunuksela (1977).

Neurolepetanaesthesia did not impair the circulatory function, in agreement with Corssen et al. (1965), Corssen (1966) and Zindler (1966). The heart rate, arterial blood pressure and rate pressure product were decreased denoting reduced afterload which decreases myocardial oxygen demand in agreement with Maunuksela (1977). The rate pressure product was calculated to reflect the oxygen consumption of the heart indirectly (Kitamura et al., 1972). Dehydrobenzperidol fentanyl combination is known to cause dilatation of the resistance and capacitance vessels (Dixon et al., 1970). The study of Sonntag et al. (1972) showed that dehydrobenzperidol alone increased the heart rate significantly with a slight decrease of blood pressure and an increased myocardial oxygen consumption. Subsequent injection of fentanyl antagonised these changes and myocardial oxygen consumption returned to control levels.

The present study showed that halothane is associated with insignificant changes in arterial blood pressure, heart rate, rate pressure product and central venous pressure, in agreement with Maunuksela (1977). In contrast to our findings, halothane was reported to cause substantial falls in blood pressure in cardiac patients (Jacobson et al., 1970) and to cause more hypotension than neuroleptanaesthesia (Corssen et al., 1965; Conahan et al., 1973). But these authors used D-tubocurarine which has histamine release and ganglion blocking effects while we used pancuronium as the relaxant.

During cardiopulmonary bypass, the present study showed non-significant differences as regards the arterial blood pressure. During the whole surgery, the two anaesthetic techniques did not differ in regard to urine output, serum potassium concentrations, pH or blood gas tensions.

Although the present study reveals that both neuroleptanaesthesia and combined halothane anaesthesia are acceptable techniques for cardiac surgery with no differences in regard to the circulatory responses and myocardial metabolic protection, the combined halothane technique looks to compete better on clinical basis. While neuroleptanaesthesia gives too light a level of anaesthesia, halothane seems a more reliable agent to ensure unconsciousness of the patient and to induced a deeper and more even level of anaesthesia and to provide an earlier post-operative communication with the patient. Gilston (1979) reports that in skilled hands, the choice of anaesthetic drugs has little influence on the results in cardiac surgery whatever its effects on a particular parameter.

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The author was licensed to practice anaesthesia in Sheffield Area by the local authorities during July-August, 1979. He wishes to thank Dr. King R. and D. Dr. Powel D., the consultant anaesthetists for giving him the chance to deal with patients under their care. Dr. King adopts the combined halothane technique while Dr. Powel uses neuroleptanaesthesia.

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THE CARDIO-VASCULAR EFFECTS OF ENFLURANE: PHARMACOLOGICAL AND CLINICAL STUDIES

By

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SUMMARY

A Study was carried out to verify the cardio-vascular effects of enflurane pharmacologically in intact animals and isolated preparations and clinically in 73 surgical patients during anaesthesia. The study also aimed to identify the possible underlying mechanisms of any cardio-vascular effects. The drug produced significant drop in arterial blood pressure which proved to be due to direct myocardial inhibition. The degree of blood pressure drop was proportional to enflurane concentration used. Parasympatholytic, adrenolytic, ganglion-blocking and histaminic effects were excluded. Although the cardiac rhythm was stable, tachycardia was always present which might be compensatory to the accompanying hypotension. Enflurane produced vaso-dilatation of systemic blood vessels including the coronaries. It was concluded that enflurane is a useful inhalational anaesthetic agent but safe cardio-vascular responses require calculated concentrations and efficient ventilation during its administration.

INTRODUCTION

Enflurane is a fluorinated ether compound which includes five atoms of fluorine and one atom of chlorine (2-chloro-1, 1, 2-trifluoroethyl — difluoromethyl ether). It is a clear, colourless, stable volatile liquid with an ethereal odour. It is neither explosive nor inflammable at anaesthetic concentrations, atmospheric. pressure and temperatures of 21-45°C. It was first tested in animals by Krantz in 1963. The first clinical trials were done by Virtue et al (1966) and the drug was marketed in 1972.

McDowell et al. (1968), demonstrated the stability of cardiac rhythm in dogs under enflurane anaesthesia even in the presence of hypercarbia. Experimenting on dogs, Byles et al. (1971) showed that enflurane produces hypotension which is more pronounced with high concentrations. They also demonstrated that it sensitizes the heart to intravenously administered epinephrine. Skovsted and Price (1972), experimenting on cats, observed that sympathetic activity is depressed following increased enflurane concentration. They postulated that enflurane acts on the pressor elements of the medullary vasomator centres but this does not contribute much in occurrence of arterial hypotension, the peripheral vascular response to sympathetic activity being preserved.

Recently, work undertaken on intact dogs has shown that enflurane depresses the cardiovascular system by as much if not more than does halothane when administered in comparable doses (Theye and Michenfelder, 1975 ; Merin et al., 1976 ; Horan et al, 1977). These effects were sometimes accompanied by comparable falls in myocardial blood flow but there was no evidence to suggest that the heart became anoxic (Merin et al., 1976).

The use of enflurane for clinical anaesthesia in man has been proved to provide cardio-vascular stability by different authors (Botty et al, 1968 ; Dobkin et al, 1968 ; Dobkin et al., 1969 ; Shimosato et al, 1969 ; Iwatsuki et al, 1970 ; Eglimez and Dobkin, 1972 ; Lippman and Reisner, 1974 ; Hulsz et al, 1976 and Lamy and Hanquet, 1976). Because minimal arrhythmias occurred during enflurane anaesthesia (Lebowitz et al, 1970 and Lippman and Reisner, 1974), it was stated by Hulsz et al (1976) that the anaesthetic was useful in patients prone to arrhythmias due to its depressant effect upon conductivity across the bundle of Hiss.

Shimosato et al (1969) reported that enflurane produces direct myocardial depression, hypotension and reduction of cardiac output. However, Lebowitz et al (1970) found hypotension to be more pronounced in patients with elevated blood pressure prior to induction and to respond adequately to decreasing the anaesthetic concentration and administration of intravenous vasopressors and fluids. Russo et al (1973) noted that the degree of hypotension was proportional to enflurane concentration.

Tachycardia was described to charecterize clinical enflurane anaesthesia by Calverley et al (1975) ; Forster and Roelofse (1976) and Smith et al. (1978).

The present work aims to verify the cardio-vascular effects of enflurane both pharmacologically and clinically and to identify the possible underlying mechanisms.

MATERIAL and METHODS

(1) Pharmacological studies :

The cardio-vascular effects of enflurane were assessed experimentally in the intact animals and isolated preparations :

(A) Experiments in the intact animals :

1. Effect on arterial blood pressure in the chloralosed anaesthetized dog.
2. Effect on arterial blood pressure after atropinisation in the chloralosed anaesthetized dog.
3. Effect on arterial blood pressure after blocking the histamine receptors in the chloralosed anaesthetised dog.
4. Effect on impulse transmission in the superior cervical sympathetic ganglion of the chloralosed anaesthetised cat (Modified Acheson and Moe technique, 1946).

(B) Experiments on isolated animal preparations :

1. Effect on cardiac contractions and coronary outflow using isolated perfused rabbit's heart preparation. (Modified Langendorff's method described by Burn, 1952)

2. Effect on cardiac contractions and the site of action using isolated perfused toad's heart preparation (Syme's technique, 1918—1919).

3. Effect and site of action on blood vessels using isolated rabbit's ear preparation.

(II) Clinical Studies :

The cardio-vascular effects of enflurane were evaluated clinically in 73 patients of different age and sex (table 1) and subjected to various surgical procedures (table 2) carried out at Zagazig university hospital. Patients proved to be medically fit at pre-anaesthetic examination. They received atropine I.M. for premedication. Anaesthesia was given using the semiclosed method and a calibrated enflurane vaporizer «Enfluretec» — «Cyprane». The following techniques were used (table 3).

1. Induction of anaesthesia with gradually increasing concentrations of enflurane in oxygen using a fitting face-mask of the Magill's attachment in adults and of Ree's modification of Ayre's T-piece in children. Anaesthesia was maintained by enflurane under spontaneous respiration.

TABLE (1) :

Age and sex distribution of surgical patients subjected to enflurane anaesthesia.

Age group (ys)	**No. of patients**	**Male**	**Female**
up to 12	13	10	3
12 — 24	21	10	12
24 — 40	25	14	10
40 — 62	14	9	5
Total	73	43	30

TABLE (2) :

Types and numbers of operative procedures performed under enflurane anaesthesia

Operative procedure	**No. of patients**
General surgery	16
Urological operations	15
Orthopoedic operations	8
Gynaecological	10
Ear-nose and throat	11
Opthalmological operations	13
Total	73

TABLE (3) :

Classification of patients according to anaesthetic techniques :

Anaesthetic Technique	**No. of patients**
Induction and maintenance by enflurane, Oxygen, under spontaneous ventilation	11
Induction by thiopentone - suxamethonium, endotracheal intubation and maintenance by enflurane, Oxygen, spontaneous Ventilation	45
Induction by thiopentone - suxamethonium, endo-tracheal intubation and maintenance by enflurane, oxygen, controlled ventilation	17
Total	73

2. Induction by thiopentone — suxamethonium followed by endotracheal intubation. Maintenance of anaesthesia by enflurane, oxygen under spontaneous respiration.

3. As the previous technique but using a non-depolarizing muscle relaxant and controlled ventilation. Neostigmine atropine is given at the end of anaesthesia for reversing the relaxant effect.

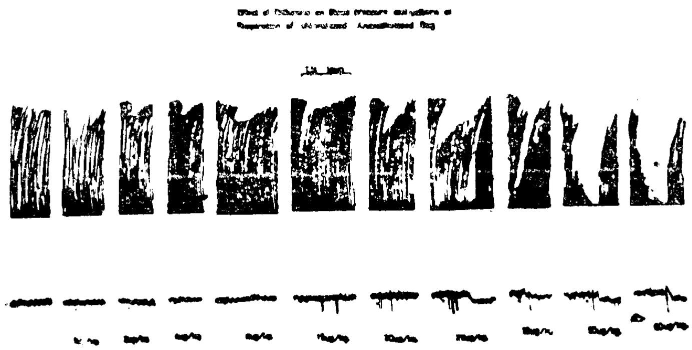
The concentrations of enflurane used ranged between 1% and 2.5%. Measured data were arterial blood pressure and pulse rate every 10 minutes with continuous monitoring of the electrocardiogram.

RESULTS

(I) Results of pharmacological studies :

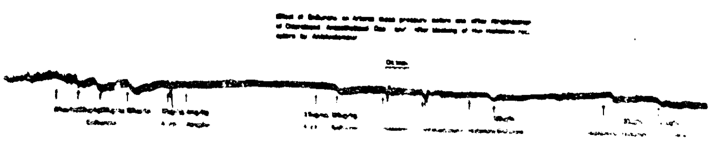
(A) Intact animal experiments

1. Effect of Enflurane on carotid arterial blood pressure of a male dog weighing 10 Kg under chloralose anaesthesia. (Fig. 1) Gradually increasing the doses of Enflurane injected intravenously produced first no change in blood pressure from doses 1-8 mg/kg then 5 mmHg reduction from doses of 15-20 ug/kg, then 10 mmHg reduction with doses from 29-36 ug/kg, then 10% reduction of blood pressure with doses of 50 ug/kg and finally 15% decrease of blood pressure with doses of 60 ug/kg body weight.



The total decrease in blood pressure throughout the whole experiment was 35 mmHg. The starting blood pressure was 110 mmHg.

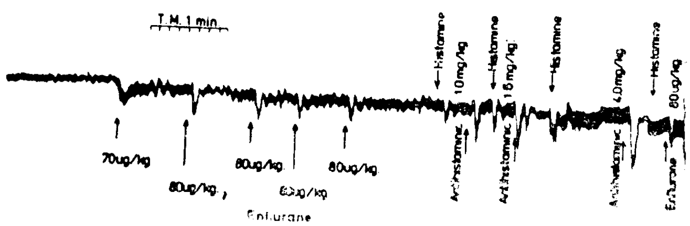
2. Effect of Enflurane on the blood pressure in the chloralosed dog after atropinisation. (Fig. 2).



The drop in carotid blood pressure produced by a dose of Enflurane of 120 ug/kg body weight was 12 mmHg and it was not modified after blocking the peripheral cholinergic receptors using a dose of atropine sulphate of 4 mg/kg body weight i.e. hypotension was not mediated through parasympathetic stimulation.

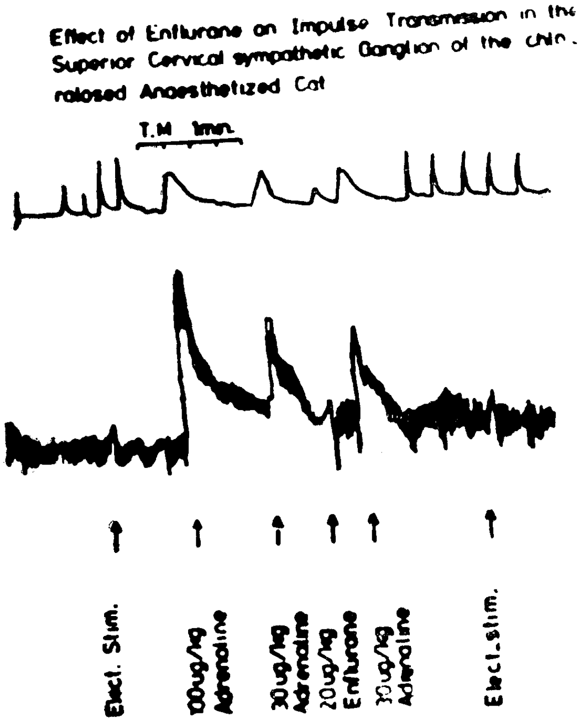
3. Effect of Enflurane on carotid blood pressure in a cholarlosed dog before and after blocking histamine receptors by an anti histaminic. (Fig. 3)

Effect of Enflurane on arterial blood pressure after blocking of the histamine receptors by Antihistaminic.



The drop in pressure caused by Enflurane was not modified by blocking the histaminic receptors by antihistaminics in a dose of 4 mg/kg body weight i.e. hypotension was not mediated through release of histamine.

4. Effect of Enflurane on impulse transmission in the superior cervical sympathetic ganglion of the chloralosed anaesthetised cat. (Fig. 4).



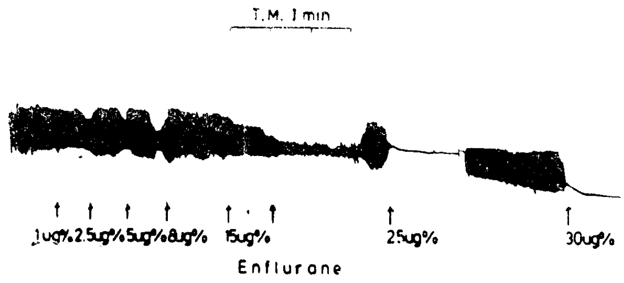
The injection of Enflurane did not modify the response of the nictating membrane to electrical stimulation or the rise of blood pressure in response to the injection of adrenaline i.e. Enflurance is devoid of an adrenolytic or ganglion blocking action.

(B) Isolated preparations.

1. Effect of enflurane on cardiac contraction and coronary outflow in the isolated perfused rabbit's heart (Fig. 5).

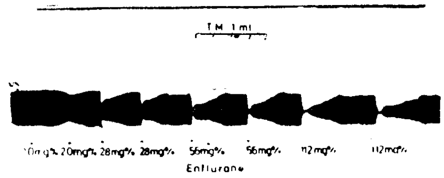
Gradually increasing concentrations of enflurane produced gradual parallel decreases in cardiac contraction with gradual increases in coronary outflow until cardiac arrest occurred.

Effect of Enflurane on cardiac contraction of Isolated perfused Rabbit's Heart



2. Effect of Enflurane on cardiac contraction of the isolated perfused toads heart (Fig. 6, Table 4)

Mode of Action of Enflurane on isolated perfused Toad's Heart (Syme's Technique)



Site of Action of Enflurane on isolated perfused toad heart (Syme's Technique)

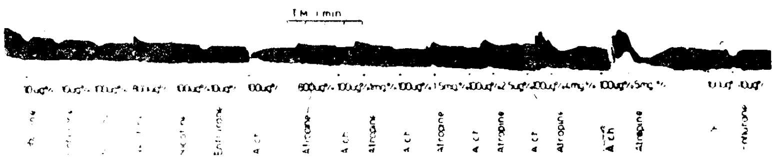


TABLE (4):

Effect of enflurane on cardiac contraction and coronary outflow of the isolated rabbits heart preparation

Dose (ug%)	Cardiac contraction (% inhibition)	coronary outflow (% increase)
1.0	NIL	NIL
2.5	17	10
5.0	55	15
8.0	65	18
15.0	90	30
25.0	Cardiac arrest	

Gradually increasing concentrations of enflurane produced gradual reductions in the amplitude of cardiac contraction. The site of action proved to be direct on the myocardium .

3. Effect of enflurane on blood vessels of the isolated rabbit's ear preparation (table 5)

TABLE (5) :

Effect of enflurane on blood vessels of the isolated rabbit's ear preparation

Dose (mg %)	**Rate of outflow/min.**	**% increase in rate of outflow**
17	4.4	10
28	4.4	10
56	4.8	12
112	4.8	12
190	4.8	12
244	5.0	22.5
280	5.5	37.5

Gradually increasing concentrations of enflurane produced gradually increasing rates of outflow from the vessels, a direct effect on the vessel wall.

II. Results of clinical studies :

Tables (6—10) demonstrate the cardiovascular. changes in surgical patients with different age groups under enflurane anaesthesia. Although enflurane produced significant hypotension and tachycardia in all age groups with different anaesthetic techniques these changes responded adequately to decreasing enflurane concentration and administration of I.V. fluids and vasopressors. It was noted that induction of anaesthesia with thiopentone produced more tachycardia and less hypotension than when anaesthesia

TABLE (6) :

Means of cardiovascular changes — in surgical Patients with different age under Enflurane anaesthesia.

No. of patients	Age (years)	Mean duration of anaesthesia ± S.E. min.	Pulse rate changes: Mean change per minute ± S.E.	Pulse rate changes: AV. time of onset of max. change ± S.E. (min)	Pulse rate changes: Mean duration of Maximal change ± S.E. (min.)	Blood pressure changes: Mean change ± S.E. mmHg	Blood pressure changes: AV. time of onest of maximal change ± S.E. (min)	Blood pressure changes: Mean duration of maximal change ± S.E. (min.)
13	up to 12	52.8±5.7884 (10—120)	11.8 ±2.3 (—10+36)	17.3±2.567 (3—50)	22.6±4.13356 (7—75)	—6.7 ±1.5413 (—35+20)	24.4 ±2 (5—50)	14.7 ±1.29 (10—32)
21	12—24	68.2±0.445 (30—105)	25.4 ±1.457 (—26+54)	17.9±1.007 (5—40)	19.4±1.77 (5—55)	—4.7 ±1.1 (—40+30)	25.95±2.99 (10—45)	19±2.3 (5—50)
25	24—40	63.4±2.2 (30—100)	21±1.7 (—30±56)	20.4±2.859 (5—90)	17.9±2.165 (5—50)	—9.166±147 (—50+25)	23±2.33 (5—80)	18±1.9 (5—50)
14	40—62	75±1.93 (30—130)	31±0.68 (12—50)	17.6±2.536 (5—54)	12.8±1.76 (5—35)	—7.9 ±1.977 (—50+30)	28.5 ±2.8 (5—70)	21±2.04 (5—45)

TABLE (7) :

Means of cardiovascular changes — in surgical Patients with open induction by Enflurane and with thiopentone induction under Enflarone anaesthesia

No. of patients	Technique of anaesthesia	Mean duration of anaesthesia ± S.E. min.	Pulse rate changes			Blood pressure changes		
			Mean change per minute ± S.E.	AV. time of onset of max. change ± S.E. (min)	Mean duration of Maximal change ± S.E. (min.)	Mean change ± S.E. mmHg	AV. time of cnest of maximal change ± S.E. (min)	Mean duration of maximal change ± S.E. (min.)
62	Induction by sodium thiepenton and succinyl choline (semi-closed technique)	71.5±0.874 (28—120)	25.4±1.2 (—30+50)	19.733±1.357 (5.90)	19.6±1.35 (5—60)	— 5.65±0.63 (—30+50)	26±1.556 (5—95)	19.7±1.175 (5—45)
11	Induction by Enflurane	23.4±2.6 (5—55)	6.4±2 (—15+16)	17.6 ±4.5 (10—50)	9.2+1.32 (7—15)	—13.8 ±1.27 (—10—25)	14.4 ±2.2 (5—25)	14.8±2.6 (3—32)

TABLE (8) :

Means of cardiovascular changes — in surgical Patients with different techniques (Spontaneous or Controlled respiration) under Enflurane anaesthesia.

No. of patients	Technique of anaesthesia	Mean duration of anaesthesia ± S.E. min.	Pulse rate changes			Blood pressure changes		
			Mean change per minute ± S.E.	AV. time of onset of max. change ± S.E. (min)	Mean duration of Maximal change ± S.E. (min.)	Mean change ± S.E. mmHg	AV. time of onset of maximal change ± S.E. (min)	Mean duration of maximal change ± S.E. (min.)
56	Semiclosed technique with spontaneous breathing	60±1.118 (10—120)	20±0.357 (—30+50)	16.96±0.9205 (5—50)	18±1.347 (5—75)	—6.5±0.324 (—50+30)	22±1.5 (5—95)	17.8±0.7896 (5—45)
17	Semiclosed technique with controlled respiration	78.7 ±1.013 (20—165)	33.7 ±4.4 (—20+56)	24.2 ±3.14 (5—90)	14.9 ±2.25 (5—35)	—8.8±1.3 (—50+30)	31.6 ±1.879 (10—50)	21.2±2.12 (5—50)

TABLE (9) :

Effect of Enflurane on pulse rate in patients with different age groups

Age group	up to 12 years		12—24 years		24-40 years		More than 40-years	
No. of cases	13 cases		21 cases		25 cases		14 cases	
	Prean.	Postan.	Prean.	Postan.	Prean.	Postan.	Prean.	Postan.
No. of observations	13	90	21	159	24	191	12	104
Sum of values	1324	10131	2018	18284	2164	20360	992	10631
Arithmetic mean	101.8	111.3	96.0952	114.9437	90.1666	106.6	82.66	102.22115
Standard deviation S.D.	3.5118	4.7246	7.8983873	5.98891	7.3009827	34.51451	4.8476	7.146
Standard error S.E.	0.97	0.495	1.72370	0.4749518	1.4903968	2.4973	1.39940	0.7007
Reliability of S.E.	Reliable	Reliable	Reliable	Reliable	Reliable	Reliable	Reliable	Reliable
«t» value	7.5001		1.59060		2.5142		8.9445	
Probability from student's «t» tables	<0.005		<0.005		<0.005		<0.005	
Significance of difference	Very highly significant		Very highly significant		Very highly significant		Very highly significant	

Prean. = Preanaesthetic.
Postan. = Postanaesthetic.

TABLE (10) :

Effect of Enflurane on Blood pressure in patients with different age group.

Age group	up to 12 years		12—24 years		24-40 years		More than 40-years	
No. of cases	13 cases		21 cases		25 cases		14 cases	
	Prean.	Postan.	Prean	Postan	Prean.	Postan.	Prean.	Postan.
No. of observations	13	90	21	159	24	1922	12	104
Sum of values	1500	9868	2435	17430	3005	22629	1550	11612
Arithmetic mean	115.4	109.6	115.95238	109.62264	125.20833	117.85938	129.1667	111.653
Standard deviation S.D.	4.64578	15.2	5.113707	6.5771276	4.73336	8.7411885	7.385	13.644
Sandard error S.E.	1.2835	4.205	1.11590	0.5216	0.9663168	0.63084	2.132	1.3379
Reliability of S.E.	Reliable	Reliable	Reliable	Reliable	Reliable	Reliable	Reliable	Reliable
«t» value	3.929539		4.2540363		4.1348957		4.3348	
Probability from student's «t» tables	<0.005		<0.005		<0.005		<0.005	
Significance of difference	Very highly significant		Very highly significant		Very highly significant		Very highly significant	

Prean. = Preanaesthetic.
Postan. = Postanaesthetic.

was induced by open enflurane. It was also noted that enflurane anaesthesia was characterized by a stable cardiac rhythm when inhaled concentrations did not exceed 2.5%. It did not cause sensitization of the heart to subcutaneously injected epinephrine in a dose of 1 ml/kg of 1/100.000 solution for 10 minutes period provided adequate ventilation.

DISCUSSION

The results obtained in the present study concerning the cardiovascular effects of enflurane support the general view that halogenated inhalational anaesthetics have a certain predilection to the cardio-vascular system.

The present work has demonstrated a significant drop in the arterial blood pressure in both experimental and clinical studies and in the latter the drop occurred irrespective of age, sex, method of induction or anaesthetic technique. The degree of hypotension has been found proportional to the used concentration of enflurane. These findings are in agreement with clinical studies of virtue et al (1966), Shimosato et al (1969), Lebowitz et al (1970) and Russo et al (1973), and experimental studies by Theye and Michenfelder (1975), Merin et al, (1976) and Horan et al (1977).

The present work tried to verify the mechanism of drop of arterial blood pressure caused by enflurane. In the intact anaesthetized dog, enflurane induced hypotension was not modified after blocking parasympathetic receptors by atropine or histaminic receptors by an antihistaminic, findings which exclude both these mechanisms. Enflurane did not modify the response of the nictating membrane of the anaesthetized cat to electrical stimulation of he superior cervical sympathetic ganglion or the rise of blood pressure in response to injected adrenaline. This proved that enflurane is devoid of an adrenolytic or ganglion blocking effect. Skovsted and Price (1972), suggested that the drop in arterial blood pressure might be due, in part, to blocking the pressor elements of the medullary vaso-motor centres. The present study showed that enflurane produced a direct depressant action on the cardiac contraction of the rabbit's and toad's heart and a vasodilator effect on the peripheral blood vessels including the coronaries. Merin et al (1976) reported falls in myocardial

blood flow of enflurane anaesthetized dogs. However, different animal species do show variations, for exemple heart rate does not progressively rise in dogs (Merin et al, 1976 ; Horan et al, 1977) wheras it does in man (Calverley et al, 1975 ; Forster and Roelofse, 1976 ; Smith et al, 1978).

The present study demonstrated that enflurane produced tachycardia in agreement with Calverley et al. (1975) irrespective of age, sex, mode of induction or anaesthetic technique. As the study proved that enflurane is devoid of any autonomic effects, tachycardia might be a compensatory reaction to the accompanying hypotension.

In the present study, the electro-cardiogram did not record arrhythmias attributed to enflurane anaesthesia, in agreement with Lebowitz et al (1970), Lippman and Reisner (1974) and Hulsz et al (1976). Calculated doses of injected adrenaline did not sensitize the myocardium to the effect of enflurane.

It can be concluded that enflurane is a useful anaesthetic agent. Safe Cardiovascular responses require calculated concentrations and efficient ventilation.

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COMPARATIVE STUDY ON THE ANTIDYSRHYTHMIC ACTIVITY OF LIDOCAINE, ETIDOCAINE AND MEPIVACAINE

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SUMMARY :

While monitoring one hundred and twenty patients during spontaneous halothane anaesthesia, different types of dysrhythmias were recorded.

Local analgesic drugs especially those with an amide group are used as anti-dysrhythmic agents. In the present work lidocaine and two other related drugs mepivacaine and etidocaine are investigated for their anti-dysrhythmic properties. Lidocaine was taken as the standard agent to convert dysrhythmia.

The comparative study revealed that etidocaine is as effective as lidocaine. Its effect is more rapid, while its dose is only one quarter that of lidocaine. Mepivacaine had a limited value and was effective only in cases of unifocal ventricular premature beats. The pharmacological properties of each drug are discussed.

INTRODUCTION

Halothane, a most useful safe anaesthetic, is used with considerable frequency. It is successfully used in cardiac surgery inspite of the spontaneous appearance of several types of dysrhythmias. A considerable percentage of these dysrhythmias are of ventricular origin.

Local analgesic drugs are able to stabilize membrane permiability of the excitatory tissue in the heart and consequently increase the refractory period, prolong conduction time and depress myocardial excitability.

The useful anti-dysrhythmic property of lidocaine (xylocaine) was shown as early as 1950 by Southwroth. Subsequently the drug was increasingly used to control dysrhythmia developing during general anaesthesia. Those developing during cardiac surgery were successfully controlled by lidocaine (Hichcock and Keowin 1959 Likoff 1959 and Weiss 1960). Grossman and Lubow (1968) reported that lidocaine was effective in suppressing and terminating ventricular dysrhythmia due to various causes. Along with the clinical reports, several experimental observations did suggest and confirm the anti-dysrhythmic activity of lidocaine. The drug was found to abolish experimental dysrhythmias induced by coronary artery ligation (Harrison 1963). Also dysrhythmia induced by digitalis (Katz 1966) and those induced by catecholamines (Fearon 1968).

Since the introduction of lidocaine in the treatment of dysrhythmia many related compounds have been tested hoping to find a better drug. The first thought was towards other members of the amide group. In the present study two closely related drugs, mepivacaine and etidocaine are administered after detection of the dysrhythmia. Mepivacaine was the result of a long series of synthesis carried out by af Ekenstam 1956 in Sweden. It would appear to have few advantages over lidocaine. Its anti-dysrhythmic properties were discussed by Boettner (1970).

Etidocaine is the most recently used member of the amide esries. It differs from lidocine by the substitution of the propyl

group for an ethyl group at the amide end. Also by the addition of an ethyl group at the alpha carbon atom in the intermediate chain.

The pharmacological action of the three given drugs differ in many points. The changes in the etidocaine structure resulted in an agent which is fifty times more lipid soluble and four times more potent than lidocaine. The potency of lidocaine equals that of mepivacaine, although they have different structures.

The plasma-protein-binding of etidocaine exceeds 90%, while that of mepivacaine and lidocaine are 65—75% protein bound. The increased degree of binding to protein is believed to be responsible for increased duration of action. In terms of anaesthetic duration, etidocaine is 2—3 times longer acting than both lidocaine and mepivacaine. Among the amide group of local analgesics, lidocaine tends to be more vasodilating than both mepivacaine and etidocaine.

Lidocaine, mepivacaine and etidocaine have a pK values 7.6 to 7.8. They tend to possess a more rapid onset of action than agents whose pK are high. Yet etidocaine possesses the most rapid onset of action (Covino 1977).

After drug injection, the rapid disappearance from the blood is believed to be related to the uptake of the drug by the tissues. Highly perfused tissues as the lungs, kidneys and the heart show higher concentration of the drug. Etidocaine shows a more rapid rate of tissue distribution. The rate of tissue distribution of both lidocaine and mepivacaine is found to be similar. The relatively high rate of tissue distribution observed with etidocaine correlates with its greater human tolerance or lower systemic toxicity.

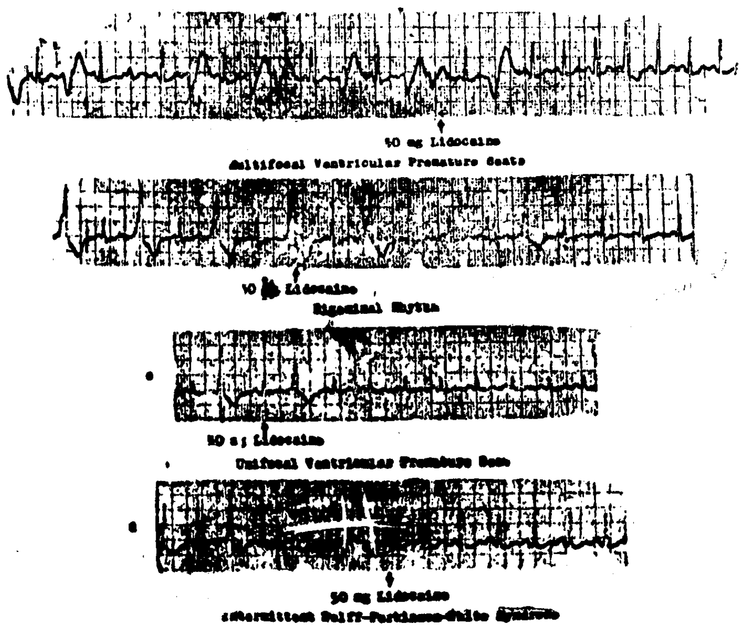
MATERIAL and METHODS

For this study one hundred and twenty patients were selected, eighty four males and thirty six females. Their ages ranged between 24 and 60 years. They were apparently fit for operations, which lasted maximally two hours.

All patients represented with regular sinus rhythm and pulse rate between 70 and 110 per minute. Their blood pressure and respiratory rate were within normal values. E.c.g. recording was available for each patient. No pre-operative medication was administered to the patients Induction of anaesthesia was done with 2.5% thiopentone sodium, a sleeping dose, to which was added 0.6 mgm atropine sulphate. Suxamethonium (75 mg) was injected intravenously to facilitate oral intubation. The patients were allowed spontaneous respiration with fresh gas flow of 8 litres/minute of oxygen : nitrous oxide in the ratio of 50 : 50%. Halothane vapour was added in a concentration of 1—3 %.

E.c.g. was recorded during induction and every five minutes during the operation. Lead II was recorded more often when dysrhythmia was observed and during its treatment.

Once dysrhythmia was detected one of the three drugs was injected intravenously as a bolus dose. The dose of both lidocaine



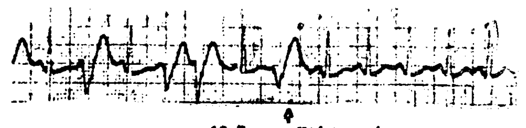
and mepivacaine was 50 mg for each drug, while the dose of etidocaine was 12.5 mg.

RESULTS

Ninety nine patients of the total one hundred and twenty patients did not develop dysrhythmia during the course of the operation. While only twent one patients (17.5%) developed different types of dysrhythmias.

1 — **Five patients** (4.16%) developed transient junctional rhythm. There was no need to abolish this abnormality as it was reversed spontanously.

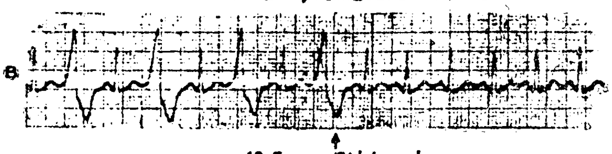
A



12.5 mg Etidocaine

Multifocal ventricular premature beats

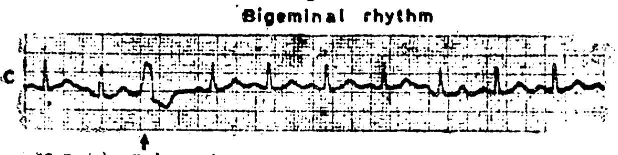
B



12.5 mg Etidocaine

Bigeminal rhythm

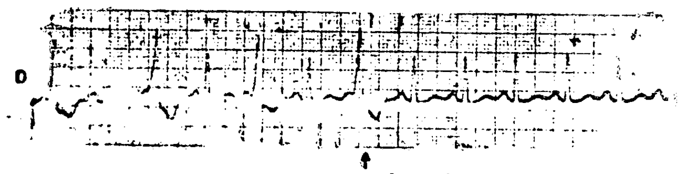
C



12.5 mg Etidocaine

Unifocal ventricular premature beats

D



12.5 mg Etidocaine

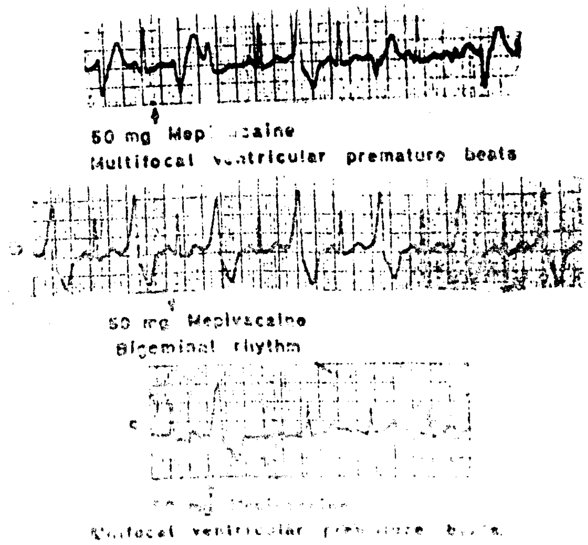
Intermittent-Wolff-Parkinson-White syndrome

2 — Two patients (1.66%) developed bigiminal rhythm. One patient was treated by lidocaine (Fig. 1b), and the dysrhythmia was abolished. The second patient was treated unsuccessfully with mepivacaine (Fig. 3b). Subsequently when etidocaine was injected sinus rhythm was observed (Fig. 2b).

3 — Two male patients (1.66%) developed intermittent Wolff-Parkinson-White syndrome. Both were successfully treated with lidocaine (Fig. 1d) and with etidocaine (Fig. 2d).

4 — Three patients (2.5%) developed multifocal premature ventricular beats. Each patient was treated with a different drug. The two patients treated with lidocaine (Fig. 1a) and etidocaine (Fig. 2a), were converted to sinus trhythm. While the patient treated wih mepivacaine (Fig. 3a) did not despond to the drug.

5 — Nine patients (7.5%) developed ventricular premature beats (unifocal). They were divided into three groups, each group of three patients. Lidocaine was injected in the first group (Fig. 1c), etidocaine in the second group (Fig. 2c) and mepiva-



caine in the third group (Fig. 3c). All nine patients responded to drug treatment.

It was interesting to find that etidocaine administration for management of dysrhythmia was rapidly followed by return to sinus rhythm. When lidocaine was administered, in similar cases, normal rhythm was observed after 1—2 minutes. The conversion to sinus rhythm was through stages of ventricular premature beats.

Mepivacaine administration, in similair cases, was the least effective. It failed to convert cases of multifocal ventricular beats or those of bigiminal rhythm. It was successful only in cases of unifocal ventricular premature beats.

DISCUSSION

Dysrhythmia is an alteration from the normal activity of the heart. It can be easily monitored by the surface electrocardiogram. There are significant dysrhythmias secondary to anaesthetic agents. Fortunately most of them are innocous, however some of them are serious. Dysrhythmia is considered to be serious if it can result in a significant decrease in the cardiac output. Also, when it may progress to cardiac arrest because of its intrinsic nature. The benign dysrhythmia should be skillfully observed, realizing that occasionally it may progress to more serious form. The serious dysrhythmia should be appropriately and aggressively treated.

Several types of dysrhythmias are observed during halothane anaesthesia. The most common are junctional (nodal) rhythm and ventricular premature beats. Rarely multifocal ventricular premature beats have been seen (Payne and Plantevin, 1962).

The reported incidence of dysrhythmia associated with halothane varies tremendously. Hudo., (1957) reported an incidence of 14% of their cases, while Stephen (1957), reported 40% of his cases. In the present work the results agree with the previous reports. Both the junctional rhythm 4.16% and unifocal vertricular premature beats (7.5%) are the most common dysrhyth-

mias. Bigiminal rhythm and Wolff-Parkinson-White syndrome, each occured in 1.6% of the cases, while multifocal ventricular premature beats were detected in 2.5% of the cases.

The incidence of the all different types of dysrhythmias was 17.5% which coincides with similair reports.

In the last few years local analgesic drugs were found to possess anti-dysrhythmic properties. When using an anti-dysrhytymic drug, it must be emphasized that a drug that is effective in treating one condition may be totally ineffective in treating another. This leads always to try to find a better new drug. Mepivacaine and etidocaine both have similar structure to lidocaine. Both of them were tested for their antidysrhythmic activity, comparing them with lidocaine.

Results of this study confirm the efficiency of the use of etidocaine as anti-dysrhythmic agent. It is more advantageous than lidocaine in many points. Its dose is only one quarter the effective dose of lidocaine. Etidocaine was efficient in the management of various types of dysrhythmias during halothane anaesthesia. The immediate reversal to the normal sinus rhythm was noticed, in contrast to the latent period of 1-2 minutes after the bolus dose of lidocaine. Restoration of normal rhythm after lidocaine was sometimes through stages of ectopic beats.

The two male patients who developed Wolff-Parkinson-White syndrome were equally successfully treated by lidocaine and etidocaine. Lidocaine was previously reported by Bigger (1970), to improve atrioventricular conduction.

Mepivacaine was the least effective drug. It was only useful in cases of unifocal ventricular premature beats. Boettner (1970) reported that the magnitude and duration of the effect of mepivacaine were less than those of lidocaine.

In view of the above findings etidocaine could be the drug of choice for the treatment of different dysrhythmias. It can be used safely during halothane anaesthesia.

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WOLFF — PARKINSON — WHITE SYNDROME CARDIAC DYSRHYTHMIA DURING HALOTHANE ANAESTHESIA

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SUMMARY :

Several types of dysrhythmia can occur during general anaesthesia. Most of these are innocous, while others are serious. While monitoring 150 patients during spontaneous halothane anaesthesia, three cases of intermittent Wolff-Parkinson-White (W.P.W.) syndrome were detected. The possible aetiology of this dysrhthmia was suggested. The importance of detection and diagnosis of the W.P.W. syndrome are discussed. The successful relief of the dysrhythmia by local analgesic drugs, lidocaine and etidocaine was reported.

INTRODUCTION

Aetiology of Wolff-Parkinson-White syndrome :

It is now generally accepted that the classic electrocardiographic abnormality is the result of pré-excitation of the ventricles. In the normal heart the P-R interval varies between 0.12 — 0.20 s.

The majority of the P-R interval is made up of the iso-electric segment between the end of the P wave and the begining of the QRS complex. The normal delay occurs at the atrial end of the atrioventricular node.

The pre-excitation of the ventricles in W.P.W. syndrome results from bypassing of the A.V. node. An anatomical basis of this bypassing was suggested by Wolferth and Wood (1933). The proposed accessory pathway from the atrium to the ventricles was called the bundle of Kent. The bypassing of the A.V. node will produce the short P-R interval. The P-R interval then usually measures 0.10 s. or less and the P wave is normal. The immediate depolarization of the ventricles will produce the delta wave of the early ventricular depolerization in association with prolonged QRS complex. The condition is often unstable, normal and abnormal complexes may alternate.

Importance of Wolff-Parkinson-White Syndrome :

There are three reasons why the W.P.W. syndrome is imortant to diagnose especially when detected during anaesthesia.

1 — Misdiagnosis of the pattern of W.P.W. syndrome :

a) The presence of broad QRS complex conduction defects of either the right or left ventricle may be suspected.

b) The appearance of Q wave simulates inferior, lateral or posterior infarction (Kariv 1958).

2 — Tendency to supraventricular tachyarrhythmia : In most patients the only other cardiac pecularity is a tendency to atrial dysrhythmia, the mechanism of which appears to be a circulating wave. The wave will use both normal and accessory pathways. Impulses will go down one way and up to the atrium using the other pass (Durrer 1970).

3 — Progress to more serious dysrhythmia : Because of the short refractory periods of the bypass, rapid ventricular rate may occur in cases of atrial flutter or fibrillation. This is seen particularly with digoxin therapy, which delays conduction in the normal pathway, the bundle of Hiss. Rapid impulses

may lead to ventricular fibrillation if the descending impulses arrive in the vulnerable phase of ventricular cycle (Drifus, 1971).

MATERIAL and METHODS

One hundred and fifty reasonably fit patients were monitored during halothane anaesthesia. No respiratory or cardiovascular abnormalities were detected. Their ages ranged from 24 to 60 years. Their Hb% was estimated not less than 70%. No pre-operative medication was administered to the patients.

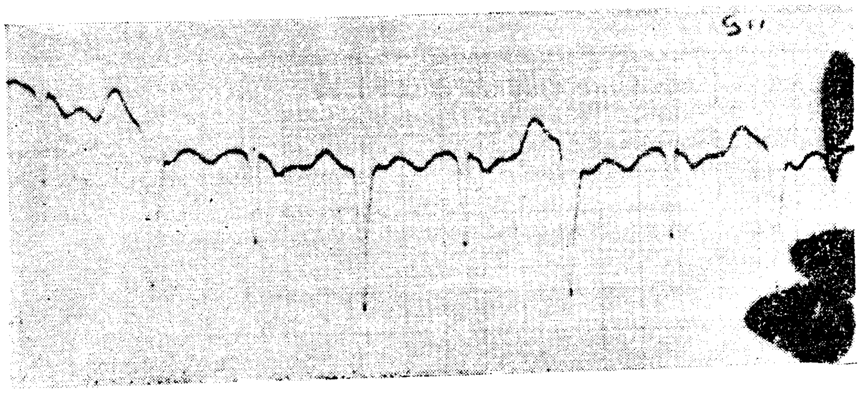
Anaesthesia was induced with 2.5% thiopentone (sleeping dose), atropine 0.6 mgm was added. Suxamethonium (75 mgm) was given to facilitate oral endotracheal intubation. Anaesthesia was maintained with nitrous oxide : oxygen (6 : 4 L/minute) together with halothane 1.5 — 2%. Patients were allowed spontaneous respiration during the whole operation.

E.C.G. was recorded pre-operatively as a basic assessment. After that Lead II was only recorded, during intubation and at five minutes interval during the operation. Once dysrhythmia was recorded, treatment started with one of the local analgesic drugs. The effect of drug administration was also documented.

All the patients for this study, presented with regular sinus rhythm. Three only of these patients (2%) developed intermittent W.P.W. syndrome during the course of the operation.

Case no. 1 : 35-year-old man was to undergo right uretrolithotomy. Pulse rate 80/minute, regular and his B.P. was 120/80. When he developed W.P.W. syndrome a bolus of 50 mgm lidocaine was administered intravenously as the line of treatment.

Case no. 2 : 40-year-old female was to undergo repair of paraumblical hernia. Her pulse rate was 82/minute regular and her B.P. 130/85. She developed intermittent W.P.W. syndrome. Her pulse rate was 115/minute after the detection of the syndrome (Fig. 1). Also a bolus of 50 mgm of lidocaine was administered intravenously.

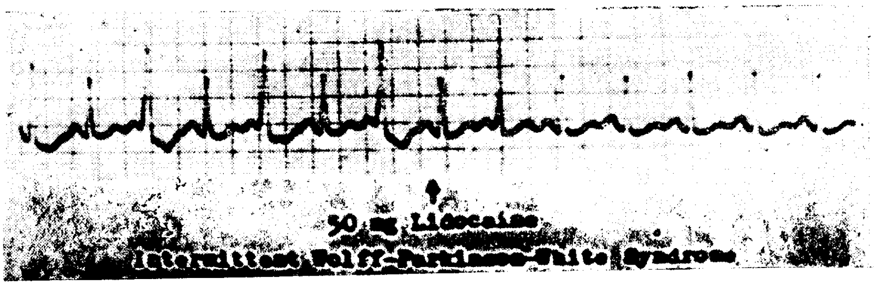


(Fig. 1)

Case no. 3 : 25-year-old male was to undero Z shape release flab of left axillary scar. He had regular pulse of 88/minute and B.P. of 130/85. When W.P.W. syndrome was observed a bolus of 12.5 mgm of etidocaine was given intravenously.

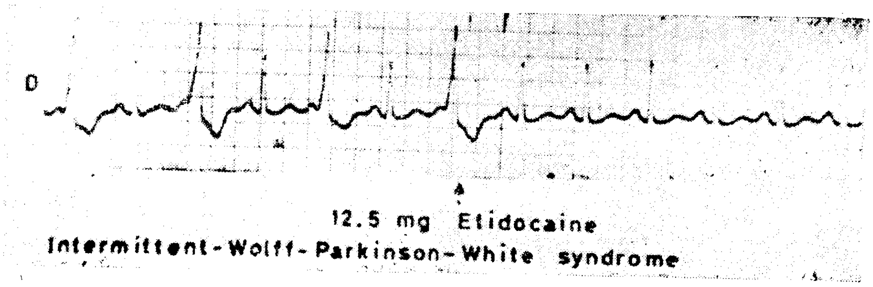
RESULTS

Lidocaine was administered in the first two cases. The sinus rhythm was resumed after a period of one minute approximately. (Fig. 2). The blood pressure did not show significant drop after lidocaine. The sinus rhythm was maintained in these two cases till the end of the operation which lasted in the two cases for another half an hour.



(Fig. 2)

In the third case, etidocaine was administered. The reversal of dysrhythmia was observed immediately (Fig. 3). Neither a drop in blood pressure, nor a recurrence of dysrhythmia was observed. The operation lasted 40 minutes after etidocaine injection. Recording of Lead II is shown in Fig. 3.



(Fig. 3)

DISCUSSION

Wolff-Parkinson-White syndrome is relatively a benign dysrhythmia. It predominantely affects males and is found in all age groups. In young subjects, it occurs mainly in individuals with no signs of heart disease. However it is found in a significant number of young patients with idiopathic hypertrophic subaortic stenosis. In older patients, this anomaly appears to result from serious heart disease, but is not always associated with a benign prognosis.

The complex sometimes occurs during cardiac catheterization, when nodal tissue might be injured. After posterior infarction, it is apparant when the nodal tissue is proved to be injured at subsequent nacropsy.

This dysrhythmia when it occurs during anaesthesia may lead to serious outcome. The misdiagnosis of the dysrhythmia, as it simulates myocardial infarction, may lead the anaesthetist to shorten the time of the operation.

The supraventricular tachycardia, commonly associated with the syndrome, needs some consideration. The haemodynamic

consquences may be profound and early treatment is desired. Digoxin, the commonly used drug, is not the ideal drug of treatment in this situation. Digoxin tends to block the conduction through the A.V. node, to facilitate the passage of impulses through other bundles.

The most common dysrhythmias seen during halothane anaesthesia are nodal rhythm and ventricular extrasystoles. W.P.W. syndrome was not reported. The depressant action of halothane was reported by many authors. Morrow and Gaffney (1961) suggested that halothane has a direct depressant action on the S.A. node. Wynands (1978) stated that halothane depresses impulse formation in the S.A. node and prolongs the functional refractory period of the A.V. node as indicated by prolongation of the A-V interval of the His bundle electrogram. This may explain the appearance of the syndrome during halothane administration.

On a theoretical basis, the best drug for treatment of supraventricular tachycardia associated with W.P.W. syndrome will be quinidine Quinidine, by its direct effect, slows conduction in the atrium. Also, by its vagolytic effect, it tends to increase the speed of conduction through the A.V. node. Campkin, (1969) and Hannington-Kiff, (1968) reported the development of supraventricular tachycardia in cases of W.P.W. syndrome during the induction of anaesthesia. Atropine increases the likelihood of the event, thus scopolamine may be the antisialagogue of choice.

In this work, both lidocaine and etidocaine were successful in abolishing the dysrhythmia. This agrees with the previous report of Hoffman and Bigger, (1971), that lidocaine may improve atrioventricular conduction impairement. The effect of etidocaine was more rapid in restoration of the normal sinus rhythm. It was restored immediately after etidocaine administration.

ACKNOWLEDGEMENT

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THE CARDIO-VASCULAR EFFECTS DF ETOMIDATE : AN EXPERIMENTAL STUDY

By

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SUMMARY

A study has been carried out, on intact animals and isolated animal preparations, to investigate the effects of the intravenous anaesthetic etomidate on the cardio-vascular system. The therapeutic dose of etomidate of 0.2 mg/kg body weight produced no hypotensive effect. Higher doses produced progressively increasing hypotension.

By investigating the possible underlying mechanisms of hypotension due to etomidate, it was shown that the drug has no histamine-like action, no ganglion blocking effect, a direct depressant effect on the properties of the myocardial muscles and a direct inhibitory effect on the smooth muscles of the walls of peripheral vessels.

INTRODUCTION

Etomidate is a potent rapidly acting hypnotic agent first introduced into clinical anaesthesia by Doenick in 1973 after animal studies done by Janssen et al (1971). It is an ethyl-imidazole carboxylate derivative not related to any previous anaesthetic agent. It has been described by Fischer et al (1978), to have the most pronounced cardiotherapeutic range. Savege (1979), maintains the idea that etomidate has little adverse effects on the cardiovascular system in clinical anaesthesia.

Janssen et al. (1975) has reported that the duration of hypnosis due to etomidate in mice, rats, guinea pigs, rabbits and dogs is dose dependant. However, Weymar et al. (1974) and Fischer et al (1978), Working on the heart-lung preparation of cats and dogs, respectively, had demonstrated that the cardiovascular depression is not dose dependant.

In contrast, Hughes and Mackenzie (1973) had proved that etomidate induces a dose related decrease in mean arterial blood pressure of the experimintal intact rabbit.

Different investigators experimenting on intact animals (Weyman et al, 1974, Tarnow et al, 1974; Skovsted and Sapthavichaikul, 1977, and Hughes and Mackenzic, 1978) and isolated preparations (Fischer et al, 1978), have demonstrated that etomidate produces minimal cardiovascular depression. However, detailed studies concerning the mechanism of cardiovascular depression are lacking.

The present work comprises a detailed study in the intact experimental animals and isolated animal preparations, in order to verify the effects of etomidate on the cardiovascular system and to elucidate the possible underlying mechanisms of action.

MATERIAL and METHODS

The cardiovascular effects of etomidate were evaluated experimentally by studying its actions in intact animals, and isolated animal preparations.

I — Intact animals :

A. Efect on arterial blood pressure in chloralosed anaesthetized dog.

B. Effect on impulse transmission in the superior cervical sympathetic ganglion of the chloralosed anaesthetized cat. (Paton, 1953 and Trendenberg 1954)

II — Isolated preparations.

A. Effect on the cardiac contraction in the isolated perefused Toad's Heart (Syme's Technique 1918—1919 described by Burn, 1952).

B. Effect on blood vessels in the isolated Rabbit's ear peperation.

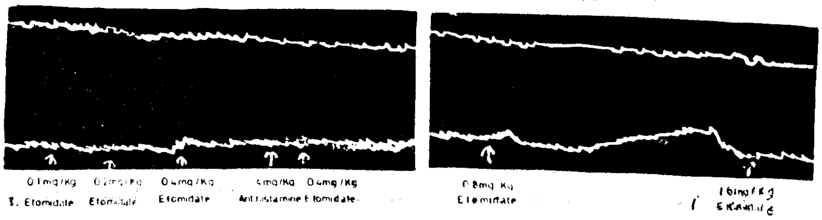
C. Efect on isolated Rabbit's aortic strip (Furchgott and Bhadrakom, 1953).

RESULTS

1 — Results in intact animals :

A — Effect on arterial blood pressure in chloralosed anaesthetized dog. (Fig. 1).

FIG (1) EFFCT OF ETOMIDATE ON ARTERIAL BLOOD PRESSURE AND RESPIRATION OF THE CHLORALOSED ANAESTHETISED DOG



Gradually increasing doses of etomidate of 0.2, 0.4, 0.8 and 1.6 mg/kg body weight produced progressive reduction in the carotid arterial blood pressure together with progressive decrease in the heart rate of 140, 120, 100 and 80 beat/min. respectively Respiration also decreased in rate and became irregular with gradually increasing the doses of the drug.

B. Effect on impulse transmision in the superior cervical sympathetic ganglion of the chloralosed anaesthetized cat. (Fig. 2).

The intravenous injection of 0.4 mg/kg of etomidate did not modify in any way the contraction of the nictitating memberane or the rise in the arterial blood pressure produced by electrical stimulation of the sympathetic trunk (10 volts maximal repetitive stimuli at a rate of 10/sec and duration of 1 millisec. maintained for 30 sec).

Also intra-arterial injection of 0.05 mg of etomidate in the external carotid artery (supplying the superior ganglion) did not modify the contraction of the nictatating membrane or the rise in the arterial blood pressure. Etomidate was thus proved to be devoid of any ganglion blocking action which can therefore be excluded from the mechanism of the hypotension accompanying its administration.

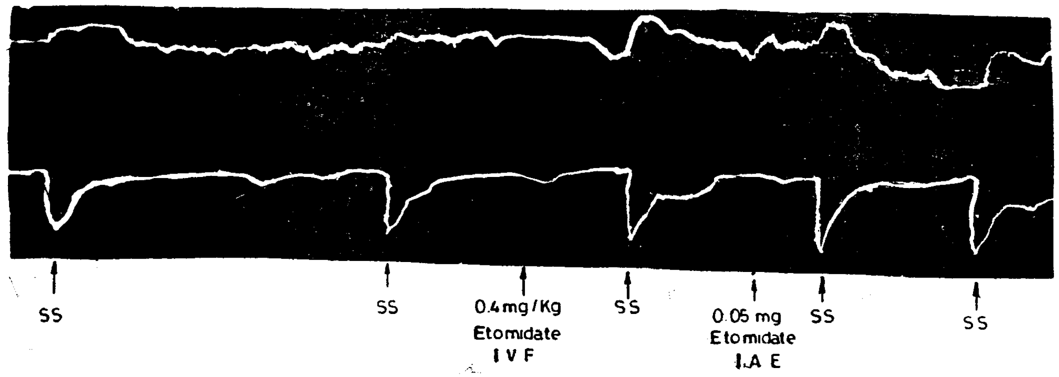
II — Results in isolated preparation :

A. Effect on the isolated perfused Toad's heart (Fig. 3).

Increasing concentrations of etomidate of 0.7, 1.5 and 3 mg% reduced the force of cardiac contraction by 50, 70, 90% respectively, while concentrations below 0.7 mg% had no effect on the force of cardiac contraction.

The depressant action of etomidate was not modified by blocking either the centeral or peripheral cholinergic receptors by full doses of nicotine and atropine respectively. This denoted a direct action of etomidate on the isolated toads cardiac muscle.

FIG (2) EFFECT OF ETOMIDATE ON IMPULSE TRANSMISSION IN THE SUPERIOR CERVICAL SYMPATHETIC GANGLION OF THE CHLORALOSED ANAESTHETIZED CAT



Upper tracing = Arterial blood pressure

Lower tracing = Response of nictitating memberane to sympathatic stimulation

SS = Sympathatic stimulation

I V F = Intravenous injection into femoral vein

I A E = Intra-arterial injection into external carotid artery

B. Effect on the rabbit's aortic strip (Fig. 4). Perfusion of rabbit's aortic strip by gradually increasing concentrations of 0.7 mg% to 6 mg% of etomidate did not induce any relaxation of the rabbit's aortic strip. This denoted absence of direct inhibitory effect of etomidate on the smooth muscle fibers of the big vessels.

FIG (3) - MECHANISM AND SITE OF ACTION OF ETOMIDATE ON ISOLATED PERFUSED TOAD'S HEART

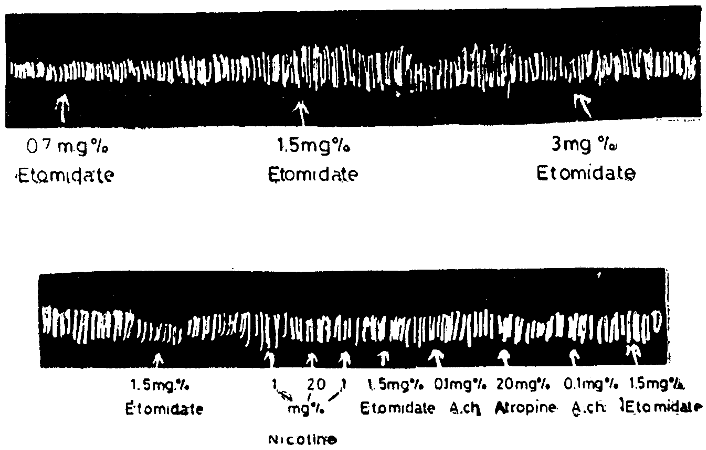
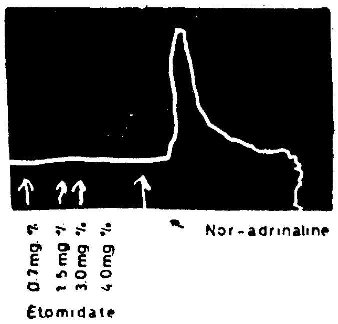


FIG (4) EFFECT OF ETOMIDATE ON ISOLATED RABBIT AORTIC STRIP PREPARATION



C. Effect on the isolated rabbit's ear preparation (Table 1).

Injection of gradually increasing doses of 2 mg, 4 mg, 6 mg, 8 mg, and 10 mg% of etomidate increased the rat of outflow by 55% to 58.3%, 63.3%, 70%, 73.3% and 83.3% respectively this denoted the vasodilator property of etomidate on the peripheral blood vessel wall.

TABLE (1) :

Effect of etomidate on rate of outflow in blood vessels of the isolated rabbit's ear preparation

Dose (mg %)	Rate of outflow ml/min	% increase in the outflow Rate
Control	55.0%	
2 mg%	58.3 %	3.3 %
4 mg%	63.3 %	8.3 %
6 mg%	70.0%	15.0%
8 mg%	73.3 %	18.3 %
10 mg%	83.3 %	28.3 %

DISCUSSION

This study has revealed that etomidate, in therapeutic doses of 0.1—0.2 mg/kg body weight does not affect the arterial blood pressure of the chloralosed anaesthetized dog. However, gradually increasing doses of 0.4—1.6 mg/kg body weight, produced progressively increasing hypotensive effects.

This dose related decrease in mean arterial blood pressure due to etomidate is in agreement with Hughes and Mackenzie (1978) working on the experimintal anaesthetized rabbit.

In a trail to investigate the possible underlying mechenisms of hypotensive effect of etomidate, the present study included expeirments on intact anaesthetized animals and isolated animal preparations.

In intact anaesthetized experimental animals, the effect of etomidate on the superior cervical sympathatic ganglion and the possibility of inducing hypotension through a histamine-like action were investigated. Experiments on isolated preparations included studying the effect of etomidate on the isolated toad's heart, the isolated rabbits aortic strip and the perfused vessels of the rabbits' ear.

The blocking of histaminic receptors of the chloralosed anaesthetized dog by a full dose of antihistaminic did not affect the hypotensive action of etomidate. This excludes a histamine-like action from the mechanism of hypotension in agreement with Doenicke et al (1973) in their clinical studies.

The contraction of the nictating membrane and the rise in arterial blood pressure in the anaesthetized cat due to electrical stimulation, was not modified after the intravenous injection of etomidate in the femoral vein or its intra-arterial injection in the external carotid artery supplying the superior cervical sympathetic ganglion. This confirmed that etomidate is devoid of a ganglion blocking action which is thus excluded from the mechanism of hypotension.

However, Stovsted and Sapthavichaikul (1977), working on cats, could demonstrate that etomidate had marked depressant effect on sympathatic activity unreflected on the arterial blood pressure. On the other hand, Hughes and MacKenzie (1978), comparing the effects of etomidate on pithed and decrebrate rabbits had proved that the cardiovascular depression return partly to a central site of action.

Perfusion of the isolated toads heart by gradually increasing doses of etomidate, was followed by progressively increasing degrees of inhibition of the force of myocardial contraction.

However, Fischer et al (1978) working on the heart-lung preparation of experimental cats and dogs have demonestrated that the cardiovascular depression, is not dose-dependant. The present work has proved a vasodilator effect on the rabbit's ear vessels although this effect has not been demonstrated in the rabbits aortic strip preparation.

Stovsted and Sapthavichaikul (1977), demonstrated that etomidate has a vagolytic effect leading to tachycardia which can compensate any hypotensive effect. The present work has shown that the drug has only a direct depressant effect. Also in the chloralozed anaesthetized dog, gradually in-creasing doses of etomidate induced dose-related decrease of heart rate.

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AN EXPERIMENTAL STUDY OF THE CARDIOVASCULAR EFFECTS OF FAZADINIUM

By

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SUMMARY

Fazadinium, has been praised among non-depolarizing muscle relaxants for its unique rapidity of onset of action. The Present study has been designed to verify the cardiovascular effects of this drug in the intact anaesthetized animals and isolated animal preparations. Fazadinium has induced a dose-dependant hypotensive effect in the chloralosed dog. It could be concluded that such a hypotensive effect is due to ganglionic blockade, central cholinergic effect on the myocardium and a depresant action on the walls of peripheral blood vessels.

INTRODUCTION

Fazadinium is a recent non-depolarizing muscle relaxant, the clinical use of which has been described by simpson et al (1972) and Arora etal (1973). The main advantage claimed for Fazadinium is its rapidity of action. One of the earliest reports suggested that the speed of onset of fazadinium was as rapid as that of suxamethonium (Blogg et al, 1973).

It is a common practice to administer suxamethonium to facilitate tracheal intubation, followed by a non-depolarizing relaxant drug for surgical relaxation. The drawbacks of this practice is that suxamethonium may cause various side effects. Instead, fazadinium, with its speed onset of action can be used for both intubation and surgical relaxation. However, the drug should prove that it is free from side-effects, mainly the cardiovascular ones.

Brittain and Tyers (1973), showed that fully effective neuromuscular blocking doses of fazadinium did not affect blood pressure, heart rate or the electrocardiogram in the anaesthetized cat. However, other authors (Marshall, 1973 ; Hughes and chapple, 1976 and Hughes et al, 1976), experimenting on cats, demonstrated that fazadinium possessed a selective atropine-like action on the cardiac vagus neuro-effector junction, when they used doses lower than those required to block neuro-muscular transmission. Hughes and chapples (1976), suggested that the vagolytic activity of fazadinium in cats relative to its neuromuscular activity correlated well with its liability to cause undesirable cardiovascular effects in man.

Fazadinium was demonstrated to induce a ganglion blocking activity in the anaesthetized cat reflected as a depressor hypotensive action, but only at doses greater than those that cause neuromuscular block (Marshall, 1973 ; Brittain and Tyers, 1973 and Hughes et al, 1976). Histamine release did not contribute in the mechanism of such hypotension in the anaesthetized cat (Brittain and Tyers, 1973).

The present work aims to verify the cardiovascular effects of the different paralysing doses of fazadinium in the experimental

intact animal as previous literature shows contradiction. It also aims to investigate the mechanism of the cardiovascular effects through a detailed pharmacological study not carried out before.

MATERIAL and METHOD

The cardiovascular effects of fazadinium were studied by using the following experiments :

1) Effect on the arterial blood pressure in the chloralosed anaesthetized dog.

2) Effect on the superior cervical sympathetic ganglion of the chloralosed anaesthetized cat (Paton, 1953 and Trendenberg, 1954).

3) Effect on the cardiac contraction in the isolated perfused toad's heart (Syme's technique, 1918—1919 as described by Burn, 1952).

4) Effect on the aortic strip of the rabbit. (Furchgoh and Bhadrakom, 1953).

5) Effect on the blood vessels of the isolated rabbit's ear preparation.

RESULTS

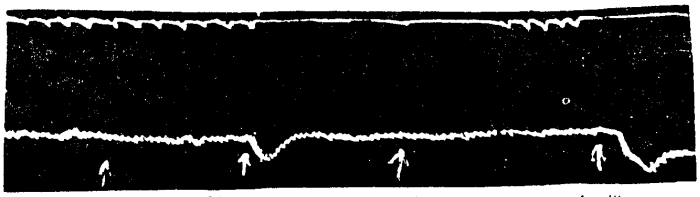
The following results were recorded :

1) Effect on the arterial blood pressure in chloralosed anaesthetized dog (Fig. 1).

In artificially ventilated anaesthetized dog, neuromuscular blocking dose of fazadinium (0.2 mg/kg), caused dose-dependent falls in blood pressure.

The fall in blood pressure was accompanied with a depression in the respiration where the dog was artificially ventilated. The depressor responses were not affected by prior administration of an antihistaminic agent (4 mg/kg).

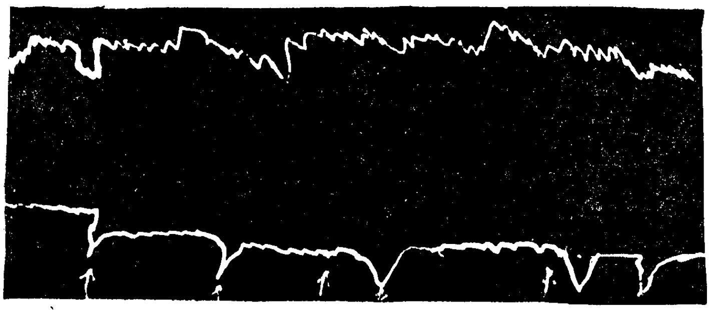
FIG (1) EFFECT OF FAZADINIUM ON ARTERIAL BLOOD PRESSURE OF THE CHLORALOSED ANAESTHETIZED DOG



2) Effect on impulse transmission in the superior cervical sympathetic ganglion of the chloralosed anaesthetized cat. (Fig. 2).

The intravenous injection of 0.5 mg/kg of fazadinium through the femoral vein, did not modify in any way the contration of the nictitating membrane or the rise in the arterial blood pressure produced by electrical stimulation of the sympathetic trunk (10 volts maximal repetitive stimuli at a rate of 10/s. and duration of

FIG. (2) EFFECT OF FAZADINIUM ON IMPULSE TRANSMISSION IN THE SUPERIOR CERVICAL SYMPATHETIC GANGLION OF THE CHLORALOSED ANAESTHETIZED CAT



Upper tracing = Arterial blood pressure
Lower tracing = Response of nictitating membrane to sympathetic stimulation
SS = Sympathetic stimulation
I A E = Intra-arterial injection into external carotid artery
I V F = Intravenous injection into femoral

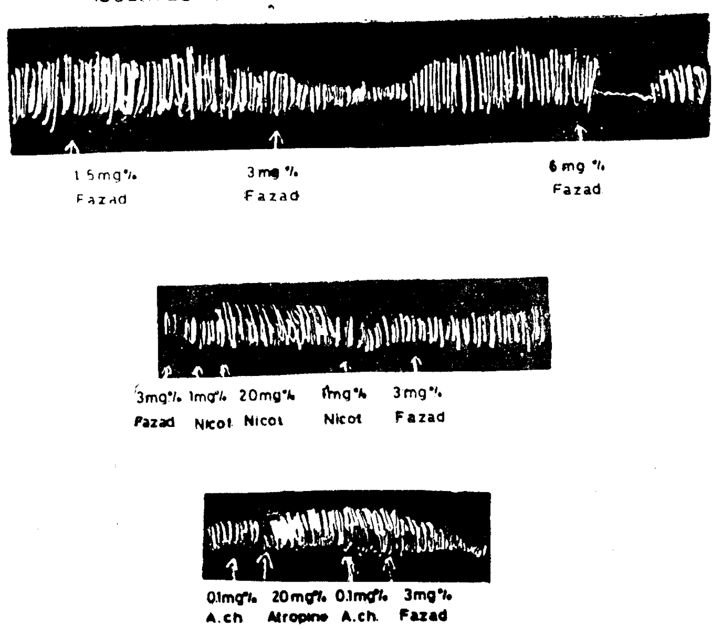
1 millisecond maintained for 30 seconds). While, intra-arterial injection of 0.2 mg/kg of fazadinium in the external carotid artery reduced contractions of the nictitating membrane induced by periodic preganglionic nerve stimulation of the sympathetic.

3) Effect on the isolated perfused toad's heart (Fig. 3).

Concenterations of fazadinium 3 mg% and 6 mg% reduced the force of cardiac contraction by 75% and 100% respectively, while concenterations below 3 mg% had no effect on the force of cardiac contraction.

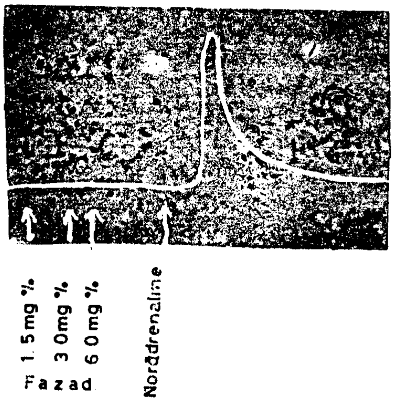
The depressant action of fazadinium was modified by blocking the central cholinegic receptors with a high concentration of nicotine (20 mg%), and not by blocking the peripheral cholinergic receptors with large dose of atropine (20 mg%).

FIG (3) MECHANISM AND SITE OF ACTION OF FAZADINIUM ON ISOLATED PERFUSED TOAD'S HEART



4) **Effect on the rabbit's aortic strip (fig. 4)** Perfusion of rabbit's aortic strip by gradually increasing concenterations of 7.5 mg% 15mg% and 30 mg% of fazadinium did not induce any relaxation of the rabbit's aortic strip. This denoted absence of direct inhibitory effect of fazadinium on the smooth muscle fibres of the big vesseles.

FIG. (4) EFFECT OF FAZADINIUM ON ISOLATED RABBIT'S AORTIC STRIP PREPARATION



5) Effect on the perfused vessels of the rabbit's ear preparation (Table 1).

Dose (mg %)	**Rate of outflow (ml/min.)**	**% increase in the outflow rate.**
Control	50 %	—
1.5 mg%	50 %	—
3. mg%	58 %	8 %
6 mg%	66 %	16 %
7.5 mg%	70 %	20 %
18 mg%	70 %	20 %

Perfusion of a dose 1.5 mg% of fazadinium had no effect on the normal rate of outflow per minute, while increasing doses 3 mg%, 6 mg%, 7.5mg% and 18 mg% of fazadinium increased the rate of outflow by 8%, 16%, 20% and 20% of the normal respectively as shown above :

The increase in the rate of outflow proved : to be due vaso dilatation action of the drug resulting from its ganglionic blocks.

DISCUSSION

The present study has demonstrated that fazadinium in the dose paralysing neuro-muscular transmission does not induse hypotensive effect in the chloralosed dog. This is in agreement with Brittain and Tyers (1973). However, larger doses induced hypotension which was a dose-dependent effect in agreement with Brittain and Tyres (1973). The schedule adopted in the present study for exploring the mechanism underlying the hypotensive effect of fazadinium included studying the possibility of a ganglion blocking effect and histamine-like action in the intact animals together with the effect on the isolated preparations of the toad's heart, the rabbit's oartic strip, and the perfused vessels of the rabbit's ear.

The present work has shown that blocking the histamine receptors of the anaesthetized dog by full doses of antihislaminics did not modify the hypotensive effect of fazadinium. This is in agreement with Brittain and Tyers (1973), who demonstrated that histamine release did not contribute in the mechanism of hypotension.

The present study has shown, in the anaesthetized cat, that a ganglion blocking effect contributes in the mechanism of hypotension. The contraction of the nictating membrane and the rise in the arterial blood pressure which occurred in response to the electrical stimutation of the preganglionic fibres of the superior cervical sympathetic ganglion of the chloralosed anaesthetized cat, was not reproduced after administration of fazadinium. This effect has taken place by using doses greater than those causing neuromuscular block. The neuromuscular blocking dose in the

anaesthetized cat was found by Brittain and Tyers (1973). to be 0.2 mg/kg body weight. This effect is a mirror-image of that demonstrated by other authors Marshall, 1973 ; Brittain and Tyers, 1973 and Hughes et al 1976) in the same type of experimental animal. In addition, our work has elucidated a central cholinergic blocking effect due to fazadinium, in the isolated toad's heart preparation. i.e. after blocking the central cholinergic receptors of the isolated toad's heart, by full dose of nicotine, fazadinium failed to induce a reduction in the force of cardiac contraction.

Marshall (1973), Hughes and chapple (1976) and Hughes et al (1976), experimenting on cats, demonstrated that fazadinium possessed a selective atropine-like action on the cardiac vagus neuro-effector junction when they used doses lower than those required to block neuro-muscular transmission. However, the present study could not confirm such an effect in the isolated toad's heart.

The present work has demonstrated that fazadinium has an inhibitory effect on the smooth muscles of the perfused vessel wall of the isolated ear preparation. It, however, had no effect on the isolated aortic strip of the rabbit.

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THE CARDIOVASCULAR EFFECTS OF ETIDOCAINE

By

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SUMMARY :

A Study was carried out to investigate the cardiovascular effects of etidocaine in the experimental anaesthetized animals and isolated animal preparations. Etidocaine in small dose of 0-125 mg/kg body weight induced a hypotensive effect. The mechanism of this hypotension has proved to include a ganglion blocking effect and a direct myocardial depressant action.

INTRODCUCTION :

Etidocaine is a new local anaethetic amide, which combines favourable properties such as rapidity of onset, a high incidence of satisfactorty anaethesia and a long duration of action in peripheral nerve blocks and extradural anaesthesia (Adams et al 1972 ; Lund et al, 1973 ; Bridenbaugh et al, 1973).

Animal experiments indicated low toxicity and good therapeutic ratio of etidocaine (Adams et al, 1972, Abdel Salam et al, 1975). During evaluation of the toxicity of etidocaine in man, scott (1975) noted that the cardiovascular alterations were minimal. Slight increases in heart rate and blood pressure were observed but these never exceeded 20% of contral values. The electrocardiogram failed to reveal any signs of rhythm disturbances. Blair (1975) noted that etidocaine reduces the tone of both capacitance and resistance vessels of the in vitro and in vivo preparations. Although, Hicks (1976) postulated that etidocaine or its metabolites or both, might exert a mild depressant effect on the myocardium, he did not demonstrate negative inotrapic effects. The central venous pressure did not reflect any venomotor changes which could be attributed to the drug.

The present work aims to study the cardiovascular responses of etidocaine in the experimental animal and the possible mechanisms of action.

MATERIAL and METHODS

The cardiovascular effects of etidocaine were studied by the following experiments :

I. The effect on the arterial blood pressure in the chloralosed anaesthetied dog.

II. The effect on impulse transmission in the superior cervical sympathetic ganglion of the chloralosed anaesthetized cat (Paton, 1953 and Trendelnberg, 1954).

III. The effect on the cardiac contraction of the isolated perfused toad's heart (Symes technique, 1918, described by Burn, 1952).

IV. The effect on isolated rabbit's aortic strip (Furchgott and Bhadrakom, 1953).

RESULTS

I. The effect on the arterial blood pressure in the chloralosed anaesthetized dog (fig. 1).

FIG. (1) EFFECT OF ETIDOCAINE ON ARTERIAL BLOOD PRESSURE IN CHLORALOSED ANAESTHETIZED DOG

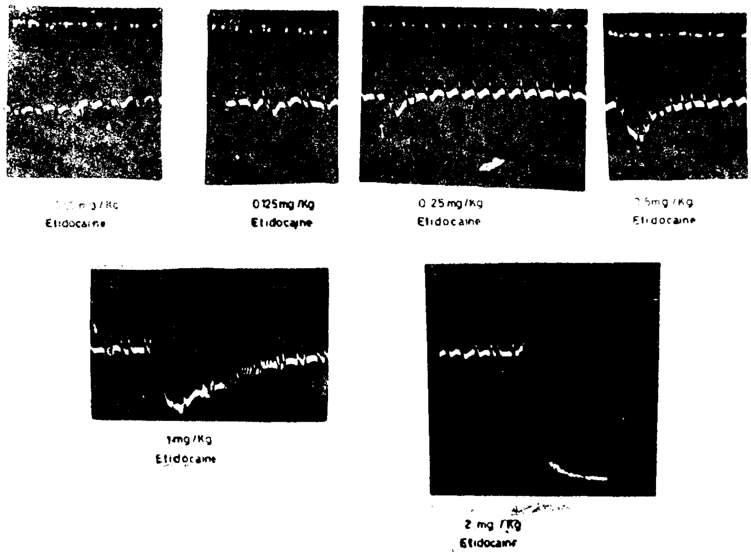
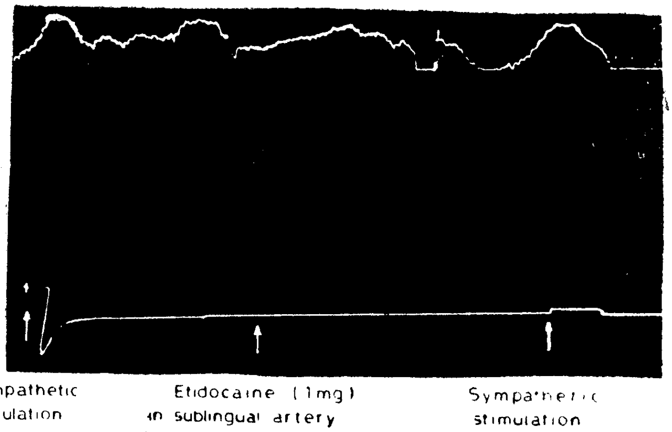


FIG. (2) EFFECT OF ETIDOCAINE ON SUPERIOR CERVICAL SYMPATHETIC GANGLION OF THE CHLORALOSED ANAESTHETIZED CAT



Upper tracing : Arterial blood pressure
Lower tracing - Response of nictating membrane to sympathetic stimulation

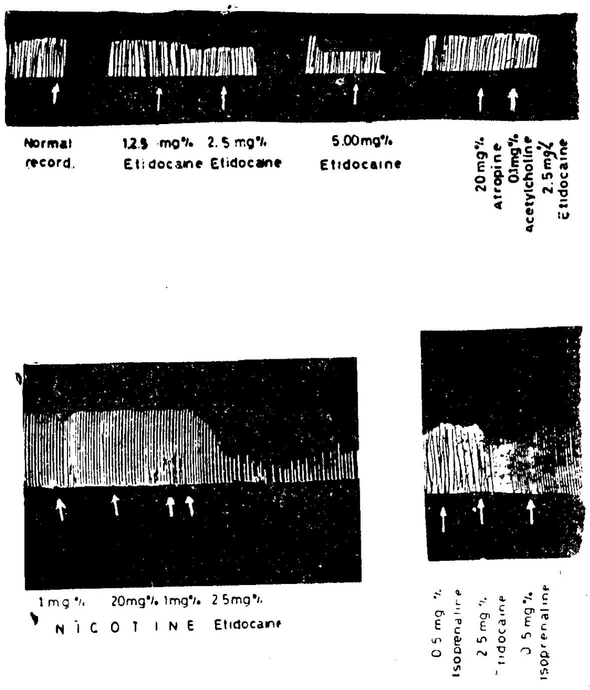
Gradually increasing doses of etidocaine, produced progressively increasing hypotensive effects.

II. The effect on impulse transmission in the superior cervical sympathetic ganglion of the chloralosed anaesthetized cat (fig. 2).

Etidocaine injected intra-arterially in the external carotid artery, in a dose of 1 mg abolished the response of the nictating membrane and the rise in arterial blood pressure produced by electrical stimulation of the sympathetic trunk (10 volts maximal repetitive stimuli at a rate of 10/sec. and duration of 1 millisec. maintained for 30 sec.)

III. Effect on the isolated perfused toad's heart (fig. 3).

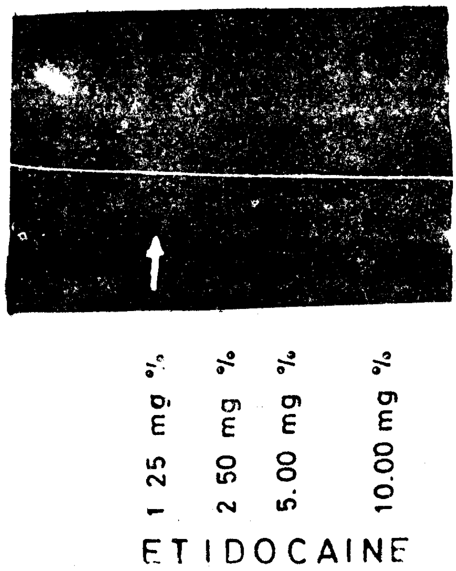
FIG. (3) MECHANISM AND SITE OF ACTION OF ETIDOCAINE ON ISOLATED PERFUSED TOAD'S HEART.



Increasing concentrations of etidocaine produced progressively increasing degrees of inhibition in the force of cardiac contraction. The site of action proved to be a direct one. There was no beta-adrenergic blocking effect, as etidocaine did not modify the isoprenaline response.

IV. The effect on isolated rabbit's aortic strip (fig. 4). Etidocaine failed to cause a relaxing effect on the smooth muscles of the rabbit's aortic strip.

FIG. (4) EFFECT OF ETIDOCAINE ON THE ISOLATED AORTIC STRIP OF THE RABBIT



DISCUSSION

The number of pubblished papers on the local anaesthetic agent, etidocaine is not very great. Still the number of those papers regarding the test of this drug in experimental animals are very

few (Adams et al, 1972 and Abdel Salam et al, 1975 and Scott et al, 1975).

The aim of the present work is to study any possible cardio-vascular effects of etidocaine in **experimental animals.**

It was noted that the drug caused hypotension in the intact dog with the occurrence of arrhythmia parallel with the dose. This hypotensive effect has been demonstrated to be mainly due to a ganglion blocking effect.

By repeating the experiments in isolated perfused toads hearts, the same depression of myocardial contractility was observed and it was proved to be due to a direct depressant effect of the drug on the heart muscle and not mediated through a cholinergic beta-adrenergic blocking or ganglion blocking activity of the drug. In our experiments, we noted also that hypotension due to large doses was accompanied by bradycaria. These results are not in agreement with observations made by Scott, (1975) who noted that tachycardia usually occurred withen 20% of the control values. But our results agree with Hicks (1976) who found direct depressant effect of the drug on the myocardium.

The abscence of any effect of the drug on the smooth muscles of the isolated aortic strip also excludes this effect as a cause of the hypotension produced and leaves only the direct depressent effect on the myocardium as the only possible hypotensive mechanism .

During our work we also noted that etidocaine has minimal respiratory depressant effects.

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SESSION II

CLINICAL ANAESTHESIA

13, December 1979

10.30 — 12.00

AHMED HABIB (M.D.)

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COMPARATIVE STUDY BETWEEN THE EFFECTS OF ALTHESIN AND THIOPENTONE SODIUM FOLLOWED BY SUCCINYL CHOLINE ON THE LEVEL OF SERUM POTASSIUM

By

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SUMMARY

Thiopentone caused more reduction in serum potassium level than althesin. Both thiopentone and althesin can be considered as useful agents to reduce the dangerous effects on the myocardium due to succinyl choline induced hyperkalaemia. Both althesin and thiopentone are useless to treat already present conditions of hyperkalaemia.

MATERIAL and METHOD

A group of 26 patients of different age and sex undergoing different surgical operations were selected for this study. This

group was free from any disease which changes serum potassium e.g. ; severe burns, crush injuries neuromuscular diseases and paralegia. This group was given althesin. Another group of 16 patients were given thiopentone sodium.

DOSES

Preoperative preparation by atropine sulphate was given intravenusly 15 minutes before induction of anaesthesia. Althesin was administered in a dose of 0.6 mg/kg. body weight, thiopentone sodium 5 mg/kg. body weight, and succinyl choline Img/kg. body weight.

SAMPLES

Three samples were taken from the anti-cubital vien each of 5 ml. The first sample (K_1) was taken after the injection of atropine. The second sample (K_2) was taken three minutes after althesin or thiopentone sodium. The third sample (K_3) was taken three minutes after succinyl choline. The serum was separated from the other components of the blood by centrifugation, the serum potassium was measured by flame photometer.

RESULTS

From figure (1) and table (I) it can be noticed that althesin caused initial drop of serum potasium by 0.05 m.Eq/L, then succinyl choline caused a rise of serum potassium level by 0.21 mEq/L, while thiopentone caused an initial drop in serum potassium by 0.09 mEq/L, then after succinyl choline there was an increase in serum potassium by 0.20 mEq/L.

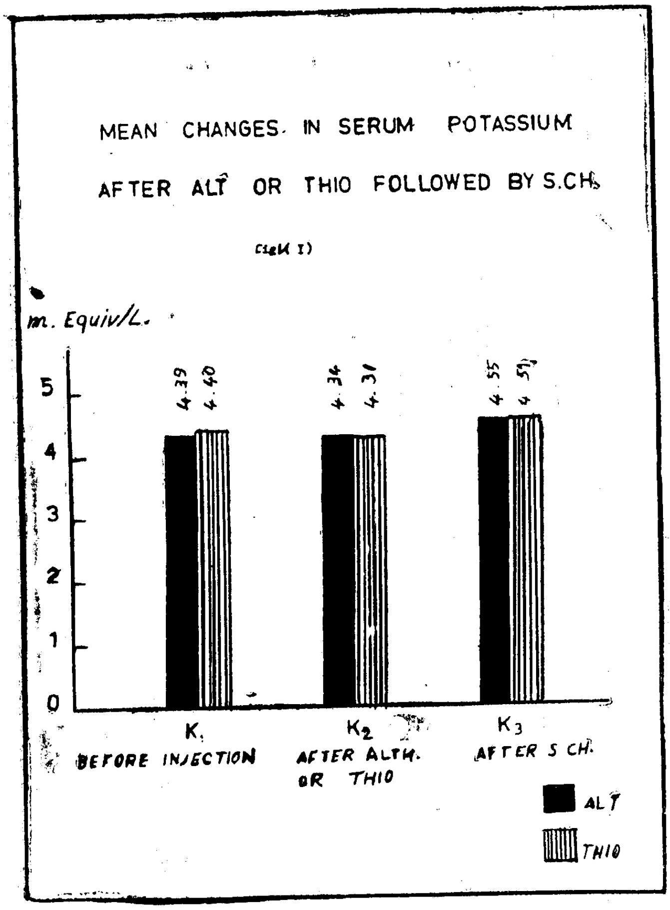
TABLE (1) :

Mean Serum Potassium Changes Due To Althesin or Thiopentone Followed By Succinyl Choline

Drug.	Statist. Items	Mean Serum Potassium mEq/L			Difference cf X values	Calculated (t) values	P $\leqslant$	Signific.
		A K_1	B K_2	C K_3				
Alt.	X	4.39	4.34	4.55	A—B=0.05	A,B=3.157	0.01	++
	S.D±	0.237	0.255	0.244	A—C=0.16	A,C=25.078	0.001	+++
	S.E±	0.046	0.049	0.0479				
Thiop.	X	4.40	4.31	4.51	A—B=0.09	A,B=10.120	0.001	+++
	SD±	0.138	0.032	0.155	A—C=0.11	A,C=9.696	0.001	+++
	SE±	0.0346	0.032	0.038				

\+ Significant
++ Highly Significant
+++ Very highly Significant.
n.s. = Not significant.

(t) tabulate at P $\leqslant$ 0.05 level = 2.262
(t) tabulate at P $\leqslant$ 0.01 level = 3.249
(t) tabulate at P $\leqslant$ 0.001 level = 4.781.



DISCUSSION

It was found that thiopentone sodium is the most intravenous anaesthetic which lowers serum potassium level while althesin and propanidid were the least to decrease serum potassium level, (Bali, 1974). This author also found in normal patients, that all changes in serum potassium returned to the control level within 10 minutes. Storner (1972) found that thiopentone, diazepam,

propanidid and halothane with N_2O/O_2 caused drop in serum potassium level, the maximum drop of which was when thiopentone was used. The drop in serum potassium level is most probably due to change in the cell membrane permeability with shift of potassium from the extracellular compartment to the intracellular space. When succinyl choline was used following the previous agents mentioned it was found that the minimum rise was present when thiopentone was used (2.5%), while the maximum rise in serum potassium was recorded after halothane, N_2O/O_2 (12.7%).

Succinyl choline induced hyperkalaemia was explained by Fahmy et al (1975) by the dynamic balance between intracellular to extracellular potassium level ratio. A relatively small percentage change in intracellular concentration may result in marked reciprocal change in serum potassium level. Furthermore, relatively small absolute changes in extracellular concentration by producing large differences in the ratio of intracellular to extracellular potassium, may have important effects on neuromuscular and cardiac physiology. Succinyl choline reduces the transemembrane potential of the motor endplate and, in doing so, changes the permeability of the membrane to sodium with efflux of potassium outside the cells. Gerald and Richard (1975) suggested that in normal muscles the motor end plate area is the only zone which contains chemosensetive receptors to acetyl choline or to its ester succinyl choline. In denervated skeletal muscle or severe burns or disuse atrophy, most or all of the muscle membrane and not the motor endplate area will act as a chomosensetive receptor to succinyl choline. The process of depolarization starts by a change in cell membrane permeability followed by potassium outflux in normal conditions but in denervated muscle there is a machine gun-like burst of potassium outflux and sodium influx, a four fold increase in muscle oxygen consumption and three fold increase in muscle blood flow. The oxygen use is increased to stimulate the $Na+/K+$ pump to restore ionic equilibrium, the resulting increased production of ATP in addition to hyperkalaemia will result in vasodilatation and increased muscle blood flow. The dangerous effects of hyperkalaemia on the heart in the form of dysrythmias, myocardial depression and cardiac arrest (Paton 1956) opened the door to study the effects of potassium on the

cardiovascular system. Thiopentone and althesin result in variable degrees of myocardial depression and peripheral vasodilatation and provide a protective mechanism against succinyl choline hyper-kalaemia either in normal and or more important, in patients with severe trauma, burns, malignant hyperpyerexia and neuromuscular disease. But these two agents cannot stop the initiation of a well established condition of hyperkalaemia which is present in cases of malignant hyperpyerexia. (Harrison 1973).

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ELECTROCONVULSIVE THERAPY UNDER ETOMIDATE ANAESTHESIA

By

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SUMMARY

In electroconvulsive therapy (E.C.T.), a preliminary barbiturate anaesthetization has become the standard procedure in most of the centres of the world. However, this paper describes a within-patient comparison of the new non-barbiturate anaesthetic drug etomidate (0.2 mg/kg.) with thiopentone (4.0 mg./kg.). Each of these two drugs was used for 112 E.C.T. sessions given to 28 psychiatric patients and careful observations were made. .The results suggest that this new drug can b used in E.C.T. whenever barbiturate anaesthesia is contraindicated.

INTRODUCTION

Electroconvulsive therapy (E.C.T.) was first introduced by Cerletti and Bini (1938) and rapidly became established as one of

the most effective treatments in psychiatry. However, the complications which occurred in electrically induced convulsions were the reason that, soon after the introduction of E.C.T., attempts were made to avoid the convulsions. The so-called «subconvulsive petit-mal response» was used (Hirschfeld, 1953; Brietner, 1957) though without therapeutic results (Kalinowsky and Hippius, 1969). The use of muscle relaxant drugs for the prevention of fractures was first recommended by Bennett (1940) who used curare which paralyzes the muscles, owing to its action on the neuromuscular junction. Neostigmine could be used as an antidote after the convulsion to shorten the effect of curare. In spite of this antidote, fatalities with all of the curare preparations were frequent, and cases became known in which the patient died before the electroshock had been given. Therefore, curare as well as tubocurarine were abandoned.

In 1952 succinylcholine, discovered by the Nobel Prize winner Bovet, was introduced for the same purpose of relaxing the muscles before an electrically produced convulsion (Holmberg and Thesleff, 1952). Succinyl-choline has no antidote, but it has the great advantage over curare that the effect of an injection usually does not last more than two or three minutes, which is sufficient for the duration of a convulsion. Succinyl-choline produces a block by depolarization with an acetylcholine-like effect. Muscular fasciculations, which may be quite painful later, are the first effect, and a feeling of suffocation indicates the begining of respiratory paralysis. It is for this reason that a preliminary barbiturate anaesthetization has become the standard procedure in most centres in the world (Heshead Roeder, 1976; Frederiksen and D'Elia, 1979).

However, succinylcholine appears to be less dangerous than the preceding barbiturate anaesthesia itself (Kalinowsky and Hippius, 1969). Therefore, Impastato (1956) devised a technique of giving the patient succinylcholine, followed by an immediate subconvulsive stimulus to prevent the feeling of suffocation. The subconvulsive stimulus is followed, after complete muscle relaxation, by the convulsive stimulus. This technique shows two disadvantages, namely that the subconvulsive stimulus may be either too weak so that the patient feels the current or too strong so that an immediate convulsion takes place before the patient is

relaxed. Therefore, this technique is reserved for patients with myocardial damage or pulmonary diseases such as asthma or emphysema, where barbiturate anaesthesia might be dangerous. Clearly however, a more superior technique should use a suitable non-barbiturate anaesthetic for such patients.

Etomidate (R (+) ethyl-1 pentyl ethyl H imidazole 5 carboxylate sulphate) may be the suitable drug as suggested by O'Carrol et al. (1977). It is a new non-barbiturate induction agent whose action is limited by rapid metabolism. Among the possible advantages of this drug is its minimal cardio-respiratory effects.

Etomidate — E.C.T. combination, therefore, should deserve a critical evaluation which has hardly been attempted so far. To this end, we carried out in a series of E.C.T.'s a within-patient comparison of etomidate with thiopentone, a barbiturate drug which is still the anaesthetic (Abramczuk and Rose, 1979) usually employed in E.C.T.

MATERIAL and METHODS

Subjects :

The study refers to 224 E.C.T. sessions given three times weekly to 28 unselected patients referred for E.C.T. from the Psychiatric Department, Zagazig University Hospitals, Zagazig, Egypt. Both sexes between 23 and 65 years of age were included. Before their first treatment, a medical history was taken and a clinical examination was carried out. No current medication was allowed throughout the trial period.

Procedure :

Premedication :

1.0 mg. atropine sulphate injected intramuscularly about one hour before induction of anaesthesia.

Anaesthesia :

Etomidate 0.2 mg./kg. or thiopentone 4 mg./kg. was I.V. injected over a period of 15 seconds into a suitable vein, usually

in the cubital fossa. The first drug used was allotted randomly and injected into a cubital vein. Wherever possible, the first drug was injected into the veins in the same arm on subsequent occasions. The second drug was always injected into veins in the other arm.

Suxamethonium :

0.5 mg./kg. was given through the same needle at 30 seconds from the start of induction or when the patient had gone to sleep.

Artificial Oxygenation :

When the muscle fasciculations had ceased, the patients were ventilated with 8L./min. 100% oxygen via a close-fitting face mask attached to a non-rebreathing valve of a Boyle's apparatus.

Each patient was ventilated for about 60 seconds then the face mask was removed and a protective mouth gag was inserted.

Application of the Shock :

All E.C.T.'s were administered in an identical way from a standard Ectron machine on setting «2» using the conventional bifronto-temporal electrode placement. After the convulsion, the mouth gag was exchanged for a Guedel airway and the patient was ventilated with oxygen, as before, until spontaneous respiration returned. The patients were turned onto their sides until consciousness returned.

Observations :

One anaesthetist was responsible for the induction of anaesthesia. Four other members of the E.C.T.-team (two anaesthetists and two psychiatrists) who collaborated in the observation of the subjects during this study, measured the following times without knowing which induction agent had been used and computations were based on the mean values of the observations made by all the four members of the E.C.T.-team.

— Swallowing time : Time from start of injection of the induction agent to the first swallowing movement.

— Apnoea time : Time from start of injection of the induction agent to first breath.

— Recovery time : Time from start of injection of the induction agent to the return of blink reflex.

— Reorientation time : The mean time from start of injection of the indction agent to the giving of correct name, hospital, day and year.

— Degree of agitation : Assessed 30 minutes after E.C.T. and scored on a 4-point scale :

0. Calm and composed
1. Talkative, unable to relax
2. Restless, pressure of talk
3. Very restless, noisy

— Scoring of side-effects : Assessment made 120 minutes after E.C.T. using 4-point scales as follows :
Headache :

0. No headache
1. Admits to slight discomfort on enquiry
2. Spontaneous mention of headache or definite agreement on enquiry
3. Severe headache, patient requesting analgesic

Nausea :

0. No nausea
1. Slight queasiness, on enquiry
2. Definite nausea
3. Severe nausea, patient may actually vomit

Giddiness :

0. No giddiness
1. Feels steadier sitting down
2. Prefers to lie down because of unsteady feeling.
3. Must lie down, too giddy to stand or walk

Muscle pains :

0. No pains
1. Admits to slight discomfort on enquiry
2. Spontaneous mention of aches and/or pains, or definite agreement on enquiry
3. Severe aches and/or pains, patient requesting analgesic

Total side-effects score : 0-12.

Close supervision and taking detailed clinical notes were a routine for all the patients. Any other side-effects or observations were also recorded using (+), (++) or (+++) to indicate their degree of severity.

RESULTS

Table I shows the description of the patients.

The mean dose of etomidate administered was 14.2 mg. (range 8.2 — 18.6 mg.) and the mean dose of thiopentone was 270.4 mg (range 164 — 372 mg.).

Etomidate anaesthesia was employed in 112 sessions. Thiopentone was also administered in an equal number of sessions.

The means of the times of swallowing, apnoea, recovery and orientation are shown in table II. An analysis of variance, according to Winer (1962) was carried out for all the observations. A summary of the results is given in table III. Etomidate had significantly shorter time-intervals than thiopentone. The F value was beyond the 0.05 point. However, the difference between patients too, was found to be significant with an F value beyond the 0.001 point. There was no significant differences between the order of administrations of the drugs (whether the drug was used first or not) nor between the diagnostic groups.

TABLE I

Description of patients

	Male	Female	Total
Diagnostic Category* :			
Depressive illnesses(1)			
Number	10	12	22
Age range (yrs)	29—60	18—65	28—65
Mean age (yrs)	51.6	55.2	53.6
Schizophrenia(2)			
Number	3	1	4
Age range (yrs)	23—44	35	23—44
Mean age (yrs)	34.0	35.0	34.3
Other psychoses and depressive neurosis(3)			
Number	1	1	2
Age range (yrs)	32	24	24—32
Mean age (yrs)	32.0	24.0	28.0
Total			
Number	14	14	28
Age range (yrs)	23—60	24—65	23—65
Mean age (yrs)	46.2	51.5	48.9
Weight			
Weight range (kgm)	49—93	41—89	41—93
Mean weight (kgm)	71.4	63.7	67.6

* Diagnostic category :

Classification according to the Egyptian Diagnostic Manual DMP—1 (Egyptian Psychiatric Association, 1975) :

Diagnostic category	Code number
(1) Depressive illnesses	06.0 and 06.4
(2) Schizophrenia	07.2 and 07.4
(3) Other psychoses and depressive neurosis	09.2 and 10.4

TABLE II

Mean times (± S.D.) of swallowing, apnoea, recovery and reorientation, in seconds, following administration of etomidate and thiopentone

Drug	Swallowing	Apnoea	Recovery	Reorientation
Etomidate	228 (±48.8)	213 (±75.6)	288 (± 97.6)	1080 (±162.3)
Thiopentone	276 (±53.2)	264 (±81.1)	306 (±114.9)	1260 (±194.8)

TABLE III

Summary of results from the analysis of variance using data from table II

	Swallowing time		Apnoea time		Recovery time		Reorientation time	
	F	$p \leqslant$	F	$p \leqslant$	F	$p \leqslant$	F	$p \leqslant$
Between patients	18.14	0.001	17.69	0.001	17.42	0.001	18.07	0.001
Drug	4.01	0.05	3.97	0.05	3.92	0.05	3.94	0.05
Order of drug administration	1.76	NS	1.58	NS	2.04	NS	1.83	NS
Diagnosis	1.32	NS	1.29	NS	1.46	NS	1.78	NS

Agitation and side-effects scores were subjected to the Student's t-test of significance. Summary of the results are given in table IV. The total side-effects scores difference between the two drugs was not significant, though muscle pains score of etomidate was significantly higher ($t = 2.04$, $p < 0.05$). Agitation score of etomidate was also significantly higher ($t = 2.68$, $p < 0.01$).

Among other observations related to the complications were the significantly greater occurrence of pain on injection ($t = 3.41$, $p < 0.001$) with etomidate, and of involuntary movements ($t = 3.38$, $p < 0.001$) and of increased muscle tone ($t = 2.64$, $p < 0.01$) after etomidate, yet no serious complications were observed.

TABLE IV

Agitation and side effects

	Etomidate Mean ± S.D.		**Thiopentone Mean ± S.D.**			
	score		**score**		**t**	**p**
Agitation	1.9	0.63	0.2	0.06	2.68	<0.01
Total side effects	2.8	0.93	2.4	0.81	1.16	N.S.

DISCUSSION

Short acting intravenous anaesthetics and muscle relaxants have long since removed the early barbaric aspects of electroconvulsive therapy (Sargant and Slater, 1972), still however, there is a need for an induction agent which is rapidly metabolised, of short duration and free from significant adverse reactions.

In this comparison of etomidate and thiopentone, a standardized anaesthetic technique was adopted for all the patients, the only variable being the induction agent. A within-patient trial was used to eliminate variations between patients.

The assessment included four parameters which measure the time from administration of the induction agent to : return of swallowing reflex, spontaneous respiration (duration of apnoea), return of blink reflex and mean times of giving correct name, name or hospital, day and year.

Swallowing reflex and apnoea time :

The return of swallowing reflex is suggested to be a useful parameter in the assessment of the return of neuromuscular coordination. It correlates significantly ($p < 0.001$) with apnoea time and is easy to measure. The short duration of apnoea (212 seconds) indicates that there is no interaction between etomidate and suxamethonium. However, prolonged apnoea is uncommon after E.C.T. (Berry and Whittaker, 1975) which facilitates respiratory recovery (Tresise, 1971). Holdcroft et al. (1976) also found no interaction between etomidate and suxamethonium.

Blink reflex :

This reflex is a convenient indicator of recovery (Boelhouwer and Brunia, 1977). It is absent during comatose states (Kimura, 1973 Shahini and Young, 1968) and blinking plays an important role in the orientation reaction (Sokolov, 1963).

Giving correct name, name of hospital, day and year :

The mean time from administration of the induction agent to giving correct name, name of hospital, day and year was regarded as the «reorientation time». The use of more elaborate tests to assess the quality of orientation, though would be more superior than simple tests of reorientation such as time to giving name (Pratt et al., 1971), might not only have prolonged the treatment sessions and disturbed other patients waiting for their treatment but might also have indicated residual action of the electro-convulsive therapy rather than a pharmacological effect.

The short mean recovery and reorientation times (288 and 1080 seconds) of etomidate indicate that it is suitable for a short procedure such as electroconvulsive therapy. It can be administered to both in-patients and out-patients who should be able to resume their normal routine in a short time.

There was no serious complications after etomidate. Complications such as involuntary movements and increased muscle tone, were less frequent and less marked than reported by other investigators (Holdcroft et al., 1976 ; Morgan et al., 1975). This

difference may be due to the use of etomidate in a dose (0.2 mg./kg.) which though induces sleep from 2—3 minutes (Brükner et al., 1974; Van de Walle et al., 1976) and is sufficient for the purpose of administration of E.C.T., it is lower than that recommended by the manufacturer (0.3mg./kg.) for induction of anaesthesia.

However, the presence of these side-effects and the occurrence of agitation after etomidate, apparently an observation which has not been the first drug of choice for induction of anaesthesia for E.C.T. in psychiatric patients. This is in keeping with the Royal College of Psychiatrists' Memorandum (1977) on the standards of administration of E.C.T. The Memorandum recommends the use of thiopentone. Nevertheless, the results of the present study suggest that the new non-barbiturate drug etomidate has the advantage that it can be used in electroconvulsive therapy whenever barbiturate anaesthesia is contraindicated.

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THE EFFECT OF GENERAL ANAESTHESIA ON THE INTRA-OCULAR TENSION IN GLAUCOMATOUS PATIENTS

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SUMMARY :

The effect of general anaesthesia on the intra-ocular pressure in glaucoma patients was investigated in 23 patients having unilateral glaucoma. Thiopentone anaesthesia induced a significant lowering in intra-ocular tension. Suxamethonium produced a transient rise, while tubocurarine significantly decreased the intra-ocular pressure. These changes were equal in the normal and glaucoma-eyes. Endotracheal intubation was associated with significant rise in the intra-ocular tension, but the increase was more consistent in the normal eye. The intra-ocular pressure was similarly decreased during halothane anaesthesia in the normal and the glaucomatous eyes, the decrease is significant only during controlled ventilation.

INTRODUCTION

The intra-ocular pressure in man is known to be a subject of many variations during general anaesthesia, and the causes of such alterations are numerous (Kornblueth et al., 1959 ; Samuel

and Be ugia, 1974). Most of the previous studies, however, were experimental or performed on healthy patients with normal intra-ocular pressure.

The present work was designed to study the influence of clinical halothane anaesthesia on the ocular tension in glaucoma-patients undergoing glaucoma operations.

MATERIAL and METHODS :

The intra-ocular pressure was measured by Schiotz tonometer which proved to be both simple and accurate as compared by other methods (Robertson and Gibson, 1968, and Wyllie et al., 1972).

Twenty three healthy patients having unilateral glaucoma and normal tension in the other eye (within the normal range of 10.5 to 20.5 torrquoted by Leydhecker et al., 1958) were selected, so that each patient was his own control, and a concent was taken from each patient before anaesthesia.

In all patients the arterial blood pressure and pulse rate were measured, then a local anaesthetic (Novosine 4% Wander) was instilled in the conjunctival sac and the ocular pressure recorded before induction of anaesthesia in both eyes.

The patients were classified into two groups according to the anaesthetic technique employed to :

I. Thiopentone, suxamethonium and halothane anaesthesia :

This study was carried out on thirteen patients (7 males and 6 females), whose age ranged from 26 to 75 years (Mean age 48 ± 19.78 years). Patients were premedicated with atropine sulfate 0.01 mg/kg, oxygenated for 3 minutes then anaesthesia was induced with thiopentone sodium 5 mg/kg slowly intravenously followed by suxamethonium I mg/kg. Oral endotracheal intubation was accomplished by direct laryngoscopy and anaeshesia was maintained by halothane 1.5% using Fluotic mark III and oxygen flow 6.0 Lt/minute. Hypoxia and hypercarbia were clinically avoided

throughout the manoeauvre through artificial ventilation during the periods of apnoea and hypoventilation. Tonometric and blood pressure measurements were made I minute after thiopentone, 1.5 minutes following suxamethonium, 30 secondes after intubation and after 15 minutes halothane anaesthesia.

2. Thiopentone, tubocurarine and halothane anaesthesia.

This included 10 patients (8 males and 2 females), whose mean age was 41 ± 12.6 years (range 32 to 68.5 years).

The patients were premedicated with atropine sulfate 0.01 mg/kg and preoxygenated for 3 minutes. Anaesthesia was induced with intravenous thiopentone 5 mg/kg followed by tubocurarine 0.4 mg/kg to achieve muscular relaxation then oral intubation was performed by direct laryngoscopy. Anaesthesia was maintained by halothane 1% and oxygen flow 6 Lt/minute. The respiration was controlled mechanically using Manley Pulmovent Model MPT, and the tidal volume was adjusted according to the individual patient needs.

The blood pressure and the intra-ocular pressure were measured I minute after thiopentone, 1.5 minutes after tubocurarine, 30 secondes after oral intubation and 15 minutes halothane anaesthesia.

RESULTS :

The changes in ocular tension of the first group are seen in table I.

Before anaesthesia the mean tension in the normal eye was 15.99 ± 2.25 torr while it was 39.64 ± 11.06 torr in the glaucoma-eye. After thiopentone anaesthesia the mean ocular pressure decreased significantly ($P < 0.05$) both in the normal eye to 13.501 ± 2.74 and in the glaucomatous eye to 30.88 ± 9.17 torry. The mean intraocular tension following suxamethonium was 17.64 ± 3.5 and 44.12 ± 12.89 torr in the normal and glaucoma-eye respectively, the changes displayed insignificant rise when compared with the preanaesthetic level. Endotracheal intubation induced a significant

TABLE I :

The effect of thiopentone, suxamethonium and halothane anaesthesia on the intra-ocular tension and arterial blood pressure (mm.Hg).

	Before anaesthesia	Thiopentone	Suxamethonium	Intubation	Halothane
Normal eye :					
Range	(12.2—20.0)	(8.54—16.48)	(15.88—23.03)	(14.57—31.8)	(12.2—20.0)
Mean ±	15.989	13.501	17.64	22.18	14.94
S.D.	2.2493	2.7379	4.503	4.33	2.935
t.		2.5314	1.4291	4.1909	1.024
P.		<0.05	>0.1	<0.001	>0.1
Degree of significance		S	NS	High S	NS
Range	(24.3—59.1)	(21.8—59.62)	(24.34—68.0)	(31.8—81.65)	(17.3—50.6)
Mean ±	39.638	30.882	44.116	52.149	34.992
S.D.	11.064	9.1668	12.892	16.195	10.378
t.		2.1972	0.9504	2.2999	1.1994
P.		<0.05	>0.1	<0.5	>0.1
		S	NS	S	NS
Arterial blood pressure :					
Range	(95—145)	(90—140)	(95—145)	(110—160)	(90—137.5)
Mean ±	117.31	111.54	123.08	138.077	112.5
S.D.	14.947	14.703	14.037	15.04	14.398
t.		1.0714	1.0141	3.5313	0.858
P.		>0.1	>0.1	>0.1	>0.1
Degree of significance		NS	NS	NS	NS

TABLE II :

The effect of thiopentone, tubocurarine and halothane anaesthesia on the intra-ocular tension and arterial lodd pressure (mm.Hg.)

	Before anaesthesia	Thiopentone	Tubocurarine	Intubation	Halothane
Normal eye :					
Range	(14.57—19.51)	(12.2—16.48)	(8.14—13.73)	(16.48—24.3)	(10.24—16.5)
Mean ±	16.759	13.921	11.654	20.339	13.947
S.D.	1.842	1.713	1.654	2.091	1.994
t.		3.3846	6.8262	3.854	3.1558
P.		0.005	0.001	0.005	0.01
Degree of significance		High S	High S	High S	S
Glaucoma-eye :					
Range	(31.32—50.62)	(21.34—13.38)	(19.51—37.13)	(37.19—59.1)	(23.1—37.10)
Mean ±	40.374	29.36	25.866	49.032	30.588
S.D.	7.232	8.654	6.264	8.538	5.886
t.		2.9298	4.5742	2.3208	3.2545
P.		<0.01	<0.001	<0.05	<0.01
Degree of significance		S	High S	S	S
Arterial blood pressure :					
Range	(105—137.5)	(105—125)	(95—110)	(110—145)	(97.5—125)
Mean ±	117.5	110.26	102.75	127.75	107.0
S.D.	10.004	7.6784	4.923	11.33	7.71
t.		1.6152	3.8476	2.124	1.675
P.		>0.1	<0.005	<0.05	>0.1
Degree of significance		NS	High S	S	NS

increase in the eye-pressure both in the normal eye (mean value 22.18±4.33 torr and $P < 0.01$), and in the glaucoma-eye (mean value 52.15±16.2 and $P < 0.05$). On the other hand, the mean intra-ocular pressure following halothane anaesthesia 14.94±2.94 torr in the normal eye and 34.59±10.38 torr in the glaucoma-eye, and the changes were statistically insignificant in either eye.

TABLE III :

Correlation coeffient, between intraocular tension and arterial blood pressure in the normal and glaucoma-eye.

	r	t value	P
Group I.			
Normal eye :			
Thiopentone	—0.0324	0.1075	NS
Suxamethonium	+0.1953	0.6605	NS
Intubation	—0.0351	0.1166	NS
Halothane	+0.0403	0.1338	NS
Glaucoma-eye :			
Thiopentone	—0.295	1.0236	NS
Suxamethonium	+0.101	0.3367	NS
Intubation	—0.2541	0.8714	NS
Halothane	+0.3317	1.1662	NS
Group II.			
Normal eye :			
Thiopentone	—0.1197	0.3410	NS
Tubocurarine	—0.2808	0.8275	NS
Intubation	—0.1394	0.3981	NS
Halothane	—0.3005	0.8911	NS
Glaucoma-eye :			
Thiopentone	—0.2111	0.6109	NS
Tubocurarine	—0.318	0.9487	NS
Intubation	—0.2939	0.8697	NS
Halothane	—0.0984	0.2797	NS

In the second group of patients, alterations in the intra-ocular tension and arterial blood pressure are illusterated in table II.

The mean pre-anaesthetic values were 16.759$\pm$1.842 torr in the normal eye and 40$\pm$374$\pm$7.23 torr in the glaucoma-eye. The ocular pressure decreased significantly to 13.921$\pm$1.713 torr in the normal eye ($P < 0.05$) and 29.36$\pm$8.654 in the glaucomatous eye ($P < 0.01$). The administration of tubocurarine displayed a high significant decrease of the intra-ocular pressure both in the normal) eye (Mean 11.126$\pm$1.654 torr and $P < 0.001$), and in the glaucomatous eye (Mean 25.866$\pm$6.264 torr and $P < 0.001$). Oral intubation induced a significant rise in the ocular tension to 20.339$\pm$2.03 torr ($P < 0.005$) and 49.032$\pm$8.538 torr ($P < 0.05$) in the normal and glaucomatous eye respectively. In this group halothane anaesthesia lowered significantly the intra-ocular pressure in the normal as well as in the glaucoma-eye (Mean value 13.947$\pm$1.949 and 30.588$\pm$5.886 torr respectively and $P < 0.01$).

There was no significant change in the Pearson product moment correlation coeffecient between the intra-ocular tension and arterial blood pressure (table III).

DISCUSSION :

The use of general anaesthesia in operative ophthalmology has increased in recent years due to the better understanding of the influences of anaesthetic agents on the intra-ocular tension, and the decreased operative and postoperative complications. In glaucoma-patients, however, the drainge and/or formation of aqueous humour is abnormally disturbed with the consequent increase in the intra-ocular tension.

In this study a decrease in the intra-ocular tension had been reported during thiopentone anaesthesia, and the degree of lowering was equally significant in both the normal and the glaucoma-eye. These results were in agreement with Sandiford, (1960) ; Adams and Barnett, (1966) Wyllie et al., (1972) ; and Hahneberegr and Graefes, (1976). They attributed the fall in intra-ocular tension to the arterial hypotension produced by thiopentone, but in this work insignificant correlation was found between the intra-

ocular and arterial blood pressures, which denotes the presence of other associated factors. In addition, the results denote that the glaucoma-eye behaves similarly to the normal eye towards thiopentone anaesthesia.

Suxamethonium induced a transient non-significant rise in the ocular pressure, and this agreed with that reported by Dillon et al. (1957) ; Schwartz and De Roth. (1958) ; Craythorne et al, (1960). These workers suggested that this rise was due to many factors including the increase in arterial and central venous blood pressures, contraction of the extraocular muscles and stimulation of the ciliary ganglion. Bowen et al.. (1978) also reported that suxamethonium increases the ocular tension even when preceeded by the administration of non-depolarising muscle relaxants.

Tubocurarine decreased significantly the inraocular tension in normal and glaucoma-eye and this result parallels that reported by Al-Abrak and Samuel (1974 b). The decrease in ocular pressure is attributed to arterial hypotension, histamine release, ganglionic blockade as well as of vasoconstriction of the choroidal vessels and decreased aqueous humour formation due to the associated lowering of the end tidal carbon dioxide levels (Samuel and Beauge, 1974). However, the present work did not show a significant correlation when tubocurarine was used.

Bowen et al. (1978) illusterated a significant rise in the ocular tension following suxamethonium administration during laryngoscopy and endotracheal intubation, and this was in conformity with our result. However, in our study the intra-ocular tension-response of the glaucoma-eye to endotracheal intubation was found less intense than in the normal eye. This is against any explanation for rise of ocular pressure during anaesthesia on basis of obstructed drainge, and it coincides with what was previously suggested about increased aqueous formation as a cause of this rise of tension due to increase in the arterial blood pressure.

Halothane anaesthesia produced lowering of the ocular tension in the normal as well as in the glaucoma-eye, however, the decrease was only significant in the group of patients receiving tubocurarine. The results are in parallal to those reported by Magora and Collins (1961) ; Munson et al., (1966) ; Maddox and

Kielor (1974) ; and Ausinsch et al., (1974). Al-Abrak and Samuel (1974a) reported a significant decrease in the intra-ocular tension during halothane anaesthesia in the patients when hyperventilated but not so when these patients were spontanously ventilated. These workers found that this difference was due to the increase in the end tidal carbon dioxide concentration in the spontaneously breathing patients during halothane anaesthesia.

From our study we may conclude that the responses of the glaucomatous eye to general anaesthesia are not totally different from the normal one. Moreover, the increase in the ocular tension is more deletorious during laryngoscopy and endotracheal intubation that at any other moment during anaesthesia. These effects are probably the results of stimulation of the sympatho-adrenal system and the marked rise in the arterial blood pressure (Serag El-Din, 1975). The increase both in the arterial blood pressure and the ocular tension can be minimised at least in part by the prior administration of tubocurarine to facilitate tracheal intubation and the achievement of controlled ventilation during the maintenance of anaesthesia to avoid any increase in the end tidal carbon dioxide level, using halothane vapour as the anaesthetic agent of choice to these glaucomatous patients.

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THE USE OF PYRIDOSTIGMINE BROMIDE FOR PROPHYLAXIS OF POST-SPINAL HEADACHE

By

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SUMMARY :

The present study has been carried out on 136 patients, divided into 4 equal groups, and undergoing minor surgical operations under low spinal analgesia. The distribution of typical and atypical spinal headaches was compared in patients with and without atropine premedication. Atropine was found to increase atypical and total headaches to significant levels. The study recommends against the routine use of atropine for premedication of spinal analgesia, a habit adopted by some anaesthetists. It gives the advice to keep atropine for treatment of bradycardia should it occur during the course of anaesthesia.

Pyridostigmine bromide circulated under the tradename «Mestinon» is indicated by Roche manufacturers in prophylaxis of headache following lumber puncture in a dose of 1 mg s.c. or I.M., 15 minutes before the puncture. The present study shows that pyridostigmine bromide decreases the incidence of typical, atypical and total headaches significantly. Further investigations are recommended to elucidate the mechanism of this effect.

INTRODUCTION :

The incidence of headache after spinal analgesia has shown a wide range of variation. Vandam and Dripps (1956), reported 11%

incidence in over 9000 spinal anaesthetics. While Harger et aL. (1976) mentioned 2-70%, Bullard et al. (1978) mentioned 2-20% incidences.

Concerning the aetiology of spinal headache, the consensus is that it results from leakage of CSF through the dural puncture site, at a rate greater than its production by the choroid plexus. The brain loses its fluid cushion and has a tendency to sag particularly in the upright position and tension is placed on pain sensitive anchoring structures.

Typical headache is occipital, at the vertex or frontal behind the eyes. It may be associated with nausea, vomiting or dizziness and is exaggerated in the upright position. It usually appears on the first to the third post-puncture day and lasts from one day to one year (Bullard et al., 1978) ranging in quality from mild to severe. Headache after spinal analgesia not showing these characteristics is described as atypical (Jones, 1974 ; Harger et al., 1976). Following spinal anaesthesia, Harger et al. (1976) reported incidences of 2.04% and 10.20% for typical and atypical headaches respectively. He demonstrated that atypical headache is more common after atropine-tranquilizer premedication than following narcotics or phenothiazines.

The anticholinestrase, pyridostigmine bromide (dimethyl-carbamic ester of 1-methyl-3-hydroxypyridinium bromide) circulated under the tradename «Mestinon» is indicated by Roche manufacturers for prophylaxis of headache following lumbar puncture in a dose of 60 mg (one tablet) or 1 mg (one ampoule) s.c. or I.M., 15 minutes before the puncture.

The present study has been designed to study the distribution of typical and atypical headaches after spinal analgesia and the ability of pyridostigmine bromide to reduce its occurrence.

MATERIAL and METHODS :

The study included 136 patients with a mean age of 36.2 (20-42) years who were undergoing minor lower abdominal and lower limb operations under spinal analgesia. They were fit candidates of spinal analgesia in regard to absence of past history

of chronic headache or migraine and being co-operative. Site of the puncture was at L_{4}-$_{5}$ space and 1.5 ml of 4% carbocaine was given to each patient in the sitting position through a midline approach. The same size of a fine spinal needle was used with the bevel in the longitudinal direction. Patients receiving more than one puncture and those whose tapped CSF was bloody, were excluded from the study. The author gave all the anaesthetics denoting the same degree of skill.

Patients were divided at random into 4 equal groups of 34 patients each. Patients of group I received 1 mg atropine 30 minutes before anaesthesia. Patients of group II received no premedication. Comparison of both groups aimed to elucidate the effect of atropine premedication on the distribution of headache after spinal analgesia. Patients of group III received 1 mg atropine and 1 mg pyridostigmine bromide 30 and 15 minutes before anaesthesia respectively. Patients of group IV received 1 mg pyridostigmine bromide 15 minutes before anaesthesia. Comparison of groups I — III and II — IV aimed to study the effect of pyridostigmine premedication on the distribution of headache after spinal analgesia.

All patients were visited by the author daily for 3 consequetive days to determine if headache symptoms have occurred. A decision to the nature of headache was then made. Headache was considered typical spinal in origin if it occurred and was aggravated in erect position and if relieved by lying flat in bed.

RESULTS :

Table I shows the distribution of types of post-spinal headache as affected by atropine premedication. Atropine significantly increased the occurrence of atypical and total headaches after spinal analgesia.

Table II shows that pyridostigmine bromide reduces significantly the incidence of typical and atypical headaches in atropine premedicated patients.

TABLE I

Distribution of headache after spinal analgesia as affected by atropine premedication.

Patient group	Premedication drug	Headache (%)		
		Typical	Atypical	Total
I	Atropine	7.7	11.9*	19.6*
II	————	7.4	9.3	16.7

* $P < 0.05$ (Significant)

TABLE II

Effect of pyridostigmine-atropine premedication on the distribution of headache after spinal analgesia.

Patient group	Premedication drug	Headache (%)		
		Typical	Atypical	Total
I	Atropine	7.7	11.9	19.6
III	Atropine/ Pyridostigmine	6.2*	7.8**	14.0**

* $p < 0.05$ (Significant)

** $p < 0.01$ (Highly significant)

Table III shows that pyridostigmine bromide reduces significantly the incidence of typical and atypical headaches in patients not premedicated with atropine.

TABLE III

Effect of pyridostigmine premedication on the distribution of headache after spinal analgesia.

Patient group	Premedication drug	Headache (%)		
		Typical	Atypical	Total
II	————	7.4	9.3	16.7
IV	Pyridostigmine	6.1*	7.5*	13.6*

* $P < 0.05$ (Significant)

DISCUSSION :

Spinal analgesia plays an important role in anaesthetic field in Egypt up till the present time. It is an easy technique which provides a cheap anaesthetic and an excellent degree of muscle relaxation, away from the hazards of general anaesthesia including explosion risk and pollution of surgical theatres by anaesthetic gases and vapours.

Since 1898, when August Bier, the father of spinal analgesia suffered and reported the first spinal headache, post-lumbar puncture headache (PLPH) has been a problem (Bullard et al., 1978).

Over the years, several techniques have been devised to lessen the occurrence of headache after lumbar puncture. Tourtellotte et al. (1964), listed alphabetically 49 methods of treating PLPH.

These included the use of fine needles, rehydration, keeping patients in recumbent position, abdominal binders, analgesics, sedatives and epidural saline injections. Gormley (1960), reported on the success of epidural injection of autologous blood to reduce PLPH, a technique which provided immediate and permanent pain relief in 89.0% and 98.4% by Digiovanni et al. (1972) and Ostheimer et al. (1974), respectively.

The present study investigates the feasibility of pyridosgtimine bromide premedication as being a simple method of prophylaxis of headache after spinal analgesia. Pyridostigmine could reduce the incidence of both typical and atypical headaches to statistically significant levels.

The ability of pyridostigmine bromide to reduce post-spinal headache is difficult to explain. Its ability to reduce typical spinal headache would suggest that the theory of CSF leakage may not be the only mechanism of headache and that other factors, including a cholinergic one, may be involved. However, pyridostigmine reduces both typical and atypical headaches whether patients are atropine premedicated or not, a finding which argues against a cholinergic role of the drug. The study recommends further investigations to elucidate the mechanism of pyridostigmine bromide in reducing headache after spinal analgesia. The ability of pyridostigmine to reduce total incidence of headache, may encourage the use of this drug for premedication of spinal analgesia.

The present study has shown that atropine premedication is followed by a higher incidence of atypical headache after spinal analgesia, in agreement with Harger et al. (1976). As many anaesthetists in our country adopt the habit of using atropine for premedication of spinal analgesia, the significant increase in total headache reported in the present study, would argue against this habit. An electrolyte infusion through a patent vein would facilitate the rapid management of bradycardia, should it occur during the course of analgesia.

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HEAT LOSS DURING ANAESTHESIA :
A STUDY AT ZAGAZIG UNIVERSITY HOSPITAL

By

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SUMMARY

A lot of enquiries arose at Zagazig university hospital concerning the suitability of the currently used ambient temperature for the anaesthetized patient. The author decided to carry out this study to determine the relationship between room and body temperature during a mean duration of three hours of anaesthesia. At ambient temperature 24-27°C, oesophageal temperature decreased significantly during the first hour and non-significant decrease continued during the second and third hours and the recovery period, but it did not reach the lower limit of normothermia. Skin temperature decreased also during anaesthesia and recovery. Rate pressure product denoted reduced oxygen consumption during the decrease in oesophageal and skin temperatures, and increased oxygen consumption during recovery. It was concluded that the ambient temperature used during the period of this study was suitable for the anaesthetized patients.

INTRODUCTION

Heat loss during anaesthesia occurs due to low environmental temperature, low humidity, infusion of cold fluids, ventilation with cold gases, exposure of body cavities, absence of muscular

movement and subcutaneous dilatation (Holdcroft and Hall, 1978).

The role of ambient temperature in heat loss of the anaesthetized patient has been studied during surface and intra-cavitary surgical procedures by Morris (1971). This worker concluded significant linear correlations of patient's oesophageal temperature with their room temperature during anaesthesia. At ambient temperature range of 24-26°C, all patients were normothermic, at 21—24°C, 30% became hypothermic and at 18—21°C, all became hypothermic. Vale (1973) reported that rooms less than 21°C with a low relative humidity, might be detrimental to patients though preferred by theatre personnel.

A lot of enquiries arose in Zagazig university hospital concerning the suitability of the currently used ambient temperature for the anaesthetized patient. This work was carried out to determine body and room temperatures at given intervals after induction of anaesthesia and to examine the effect of time on this relationship.

MATERIAL and METHODS

The subjects of the present study were 14 patients undergoing different types of surgical procedures with average duration of three hours at Zagazig university hospital during September — October, 1979. Their mean age was 25 years (18—67 ys) and their mean weight was 68.4 Kg (52—90 Kg). The anaesthetic technique entailed N2O, O2, 0.5—1.5% halothane and flaxedil with mechanical ventilation by Brompton Manely Ventilator. Room temperature was kept between 24°C and 27°C. All variables affecting body temperature were kept constant. Pre-operative oral, skin and room temperatures and intra-operative oesophageal, skin and room temperatures were measured by mercury thermometer and a digital temperature monitor (American Optical, AO). Oesophageal temperature was measured from the lower fourth of the oesophagus, being the most stable and representing the central temperature (Whitby and Dunkin, 1968). Systolic and diastolic blood pressures and heart rate were measured by bedside monitor

(AO.) Mean arterial blood pressure was calculated from the formula $\frac{\text{Systolic B.P.} + 2 \text{ diastolic B.P.}}{3}$. Rate pressure product was calculated to reflect the oxygen consumption of the heart indirectly. It equals the heart rate multiplied by the systolic arterial blood pressure and it is designated as mmHg $\times$ beat/minute $\times 10^3$ (Ketamura et al, 1973).

RESULTS

Results of the present study were tobulated in table (1) and (2) and graphed in figure (1).

Oesophageal temperature exhibited a mean fall of 0.47°C during the first hour which was significant ($P < 0.05$). During the second and third hours after induction of anaesthesia, mean falls of 0.14°C and 0.01°C were recorded which were not significant. Minimal falls of core temperature continued during recovery.

Skin temperature drop was recorded during the course of anaesthesia. Mean falls of 0.5°C, 1.2°C and 0.1°C were recorded for the first, second and third hour respectively. The drops of the second and third hours were significant. A mean fall of 0.1°C continued in the recovery period.

Mean arterial blood pressure decreased significantly in the second hour.

Pulse rate changes during anaesthesia were not significant.

Rate pressure product decreased in the second hour after anaesthesia and during recovery to significant levels.

TABLE (1) :
Means of temperature and cardiovascular changes during anaesthesia at ambient room temperature 24—27°C

Time (hours)	Oesophageal temperature (°C)	Skin temperature (°C)	Arterial blood pressure (mmHg)	Pulse rate (beat/minute)	Rate Pressure product (mmHg × beat/minute × 10 3)
Introduction	37.31	37.2	101.3	109.2	13.316
1	36.84*	36.7	98.7	131.0	12.838
2	36.70	35.5*	86.0*	122.9	10.578*
3	36.69	35.4	91.7	118.7	10.829
Recovery	36.62	35.8	95.2	124.0	13.640

* $P < 0.05$ (Significant)

TABLE (2) :
Significance of difference of mean falls in temperature and mean changes in mean arterial blood pressure

Time	Mean falls of temperature (°C)		Mean changes in mean Arterial blood pressure (mmHg)
(hours)	Oesophageal	Skin	
First	0.47 ($P < 0.05$)	0.5	— 2.6
Second	0.14	1.2 ($P < 0.01$)	— 12.7 ($P < 0.01$)
Third	0.01	0.1	+ 5.7
Recovery	0.07	0.1	+ 3.5

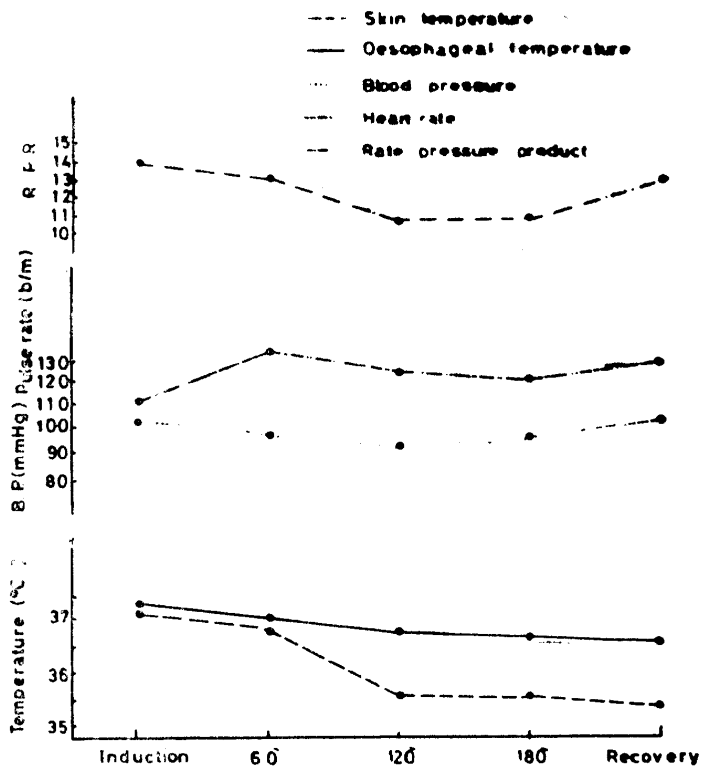

Fig (1) Means of temperature and cardiovascular changes during anaesthesia with ambient temperature 24 27 °C

DISCUSSION

Body temperature represents a balance between heat produced and heat dissipated. While heat production is a chemical process including tissue metabolism, heat loss is a physical process involving radiation, conduction and convection and depending mostly upon environmental temperature. However, body temperature is physiologically regulated by the hypothalamus. This

temperature regulation is said to remain functional during light anaesthesia (Flacke, 1963). However, muscle relaxants block increased heat production and anaesthetics cause cutaneous vasodilatation thus abolishing heat conservation, patients become poikilothermic with their temperatures dependant on environmental temperature (Morris, 1971). Reporting on patients living in cold or temporate climate, Morris (1971) found that all anaesthetized patients at ambient temperatures 24—26°C were normothermic. We hesitated to apply this conclusion because we deal with patients living in warmer environment. Wilson (1956) reported that the BMR of man decreases as a result of adaptation to warm climate. Seasonal variations in BMR are related to habits and activity patterns, the BMR being the most influencial cause of variation (Wilson, 1956 and Yoshimura, 1966).

The present study excluded variables as much as possible.

The study used one balanced anaesthetic technique. Simpson (1970) reported that ambient room temperature had no effect in influencing the patient's sensitivity to premedication drugs. Morris (1971), found no significant difference in body temperature between patients receiving ether, halogenated agents or narcotics after one or two hours. Holdcroft and Hall (1978) confirmed that anaesthetic agents do not influence temperature changes during anaesthesia.

The present work has demonstrated the largest drop of oesophageal temperature (0.47°) during the first hour of anaesthesia, in agreement with Cohen (1967) who reported an acute drop of 1°C on induction and Morris (1971), showing a mean drop of 1.3°C during the first hour. However, Holdcroft and Hall (1978), did not observe such dramatic changes in temperature in the first anaesthetic hour. This work has shown that the drop in oesophageal temperature during the second and third hours of anaesthesia is not significant, in agreement with Cohen (1967), Morris (1971) and Holdcroft and Hall (1978). On the whole, patients did not reach the hypothermic level of 36°C during the course of anaesthesia.

The present study has demonstrated that central heat loss continued during the recovery period although most of the

patients shivered during recovery. Shivering after operations is particularly related to central body temperature (Jones and Mclaren, 1965) and to halothane (Cohen, 1967). During recovery, vale (1973) gave the advice that maintenance of normothermia is essential to counteract the effects of post-operative hypoxaemia, hypotension and anaemia on oxidative metabolism. Holdcroft and Hall (1978) holds the opinion that there is little point in maintaining normothermia during anaesthesia, if heat loss occurs during transfer of the patient to the recovery area, as the most alarming heat loss occurs at the end of the operation, where anaerobiosis and lactic acidaemia constitute a final common path.

Holdcroft and Hall (1978) demonstrated that skin temperature of the anaesthetized patient drops by 0.1—0.3°C/hour. In the present study a mean fall of 0.5°C during the first hour proved to be statistically non-significant. However, a mean significant fall in skin temperature of 1.3°C occurred in the second hour, which may be due to vasoconstriction to maintain the least recorded arterial blood pressure. Holdcroft and Hall (1978) got the same observation and suggested a similar explanation.

The present work showed that the rate pressure product decreased significantly during the second hour of anaesthesia denoting a decreased oxygen consumption of the myocardium. This was quite beneficial as it paralleled the drop of both the core and shell temperatures of the body. The rate pressure product rose significantly during recovery which reflected increased myocardial oxygen consumption At recovery, there is a rapid increase in heat production. This energy is produced by the oxidation of glucose and oxygen would be consumed at more than basal rates. Failure to increase the inspired oxygen concentration or to maintain an adequate cardiac output and oxygen carrying capacity could lead to oxygen debt and acidosis.

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SESSION III

EXPERIMENTAL ANAESTHESIA

13, December 1979

12.30 — 14.00

SALAH EL-HALABY (M.D.)

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شركة الجمهورية لتجارة الأدوية والكيماويات والمستلزمات الطبية

— تأسست فى سنة ١٩٦٣ لاستيراد وتسويق الكيماويات الدوائية والمعملية والأجهزة والمستلزمات الطبية والعلمية ٠

— تقوم الشركة بتجهيز المستشفيات والوحدات العلاجية بكل احتياجاتها سواء من الأجهزة والمعــدات الطبية أو من التجهيزات المدنية كالمطــابخ والمغاسل والأسرة والثلاجات الكهربائية ومواقد وأفران البوتاجاز ٠

— كما تقوم الشركة بتوفير جميع احتياجات صناعة الدواء فى مصر من الكيماويات الدوائية ومستلزمات الانتاج ٠

— بالشركة حاليا أكبر مركز متخصص لتركيب وتشغيل وصــيانة الأجهزة الطبيـــة والعملية كما يقوم المركز بتدريب الفنيين من خريجى المعاهد والمراكز المهنية ٠

— المركز الرئيسى ٢٣ شارع السواح بالأميرية ــ القاهرة ت : ٩٦٩٣١٤ــ٨٧١٠٦٧

ادارة الاستيراد ٦ شارع الشواربى ــ القاهرة ت : ٧٥٤٣٠٩ــ٧٥٤٣٠٠

منطقة الاسكندرية ٨ شارع صلاح سالم بالعطارين ت : ٨٠٩٩٢٨ــ٨٠١٦٧٩

مخازن الكيماويات أسفل مدرجات نادى الزمالك القاهرة ت : ٨١٢٩٢٦

فروع بيع الكيماويات

— ١٥ (أ) شارع شريف ــ القاهرة ت : ٧٥٦٥٤٨

— ١٣ شارع محمود بسيونى ــ القاهرة ت : ٧٤٣٣٧٨

— شارع أديب اسحق ــ اسكندرية ت : ٨٠٨٨٣٩

— شارع طلعت حرب ــ أسيوط ت : ٣٧٢٦

— شارع الجمهورية والشهيد عبد المنعم رياض ــ بورسعيد ت : ٩١٦٤

— شارع الجيش عمارة الغرفة التجارية ــ طنطا ت : ٣١٩٢

فروع بيع المستلزمات الطبية

— عمارة بناجا ميدان باب اللوق ــ القاهرة ت : ٢٧٥٧٧

— مبنى دار الحكمة ٤٢ شارع القصر العينى ــ القاهرة ت : ٣٢٩٠٩

— ٣٦ شارع صفية زغلول ــ اسكندرية ت : ٢٧٢١٧

— ٧ شارع الأسقفية ــ اسكندرية ت : ٢٩٩٥٢

— مبنى الشركة بشارع السواح ــ الأميرية بالقاهرة (فرع القطاعى)

ANAESTHETIC ACTIVITY AND ACUTE TOXICITY STUDIES OF ENFLURANE

By

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SUMMARY

Anaesthetic activity and acute toxicity Studies have been performed on enflurane in toads.

The study of the anaesthetic activity entailed the determination of the minimal anaesthetic dose (MAD), the maximal anaesthetics dose (AD 100) as well as the anaesthetic features throught the anaesthetic range. Calculations were also made, according to the Spearman-Karber method, of the median anaesthetic dose (AD50), with its 95% fiducial limits.

Acute toxicity studies were conducted in a similar way for the determination of the minimal lethal dose (MLD), the certainly lethal dose (LD100) and the features of their toxicity. Calculations were also made for the median lethal dose (LD50) with its 95% fiducial limits. Post-mortem examination was done to verify the cause of death.

The therapeutic index was calculated from the ratio LD50 to AD50, which proved a wide safety margin for enflurane in toads.

INTRODUCTION

Enflurane is a halogenated ether compound including five atoms of fluorine and one atom of chlorine. Chemically, it is difluoro-methyl, 1, 1, 2-trifluoro-2-chloro-ethyl ether. It was tested by Krantz in 1963 who concluded that it had potent anaesthetic properties and appeared to be safe in animals (Virtue et al, 1966). In 1969, Dobkin et al, suggested its safe clinical use through an accurate vaporizer. It was marketed in 1972.

The present study is concerned with pharmacological studies of the anaesthetic activity and acute toxicity of Enflurane in experimental animals.

MATERIAL and METHOD

I — Anaesthetic Activity Studies :

Toads from the same species and a homogeneous strain (weight range : 15-25 gm), were used for pilot experiments to calculate the possible anaesthetic range of dosage. Then, they were divided into groups of equal size which were intraperitoneally injected with gradually increasing doses of Enflurane. Following the injection of each dose, animals were observed for :

1. Induction time of anaesthesia : from drug injection till loss of righting reflex.
2. Duration of anaesthesia : during which the animal could not correct its normal posture.
3. Degree of anaesthesia : light, moderate or deep as judged from the degree of muscle flaccidity, loss of reflexes and response to painful stimuli.
4. Recovery time : from inability to regain posture till the appearance of normal mobility.
5. Post-anaesthetic sequelae : as retching or vomiting.

The obtained data were tabulaed to deduce :

1. The minimal anaesthetic dose (MDA).

2. The minimal and maximal values for the certainly anaesthetic dose (AD100).

3. The full range of anaesthetic activity.

4. The median anaesthetic dose (AD50) : which was calculated after Spearman-Karber method (Rossi, 1956) for the determination of LD50 using the following modified formula :

$$\text{Log AD50} = X_k + \frac{1}{2} d - \frac{d \sum r,}{n} \text{,where,}$$

X_k = log dose causing 100% anaesthesia.

d = Log interval of doses.

$\sum$ r, = Sum of anaesthetised animals at each dose level.

n = Number of animals in each group

Then, 95% fiducial (confidence) limits for AD50 was calculated from the formula :

95% fiducial limits : Log AD50 $\pm$ 1.96 $\times$ S.E., (m.), where. 1.96 = «t» value at which the level of probability (p) of a normal frequency distribution equals 0.05, to judge the significance of the deviation.

S.E.(m) = Standard error of the Log. AD50, which equals the square root of the variance of the log. AD50 [V(m)] which can be worked out from the formula

$$V(m) = \frac{d2}{n2(n\text{-}1)} .\ r,\ (n—r), \text{ where,}$$

d2 = Squared value of og interval of doses.

n2 = Squared value of the number of animals in each group.

r_i = Sum of anaesthetized animals at each of the initial dose levels.

r_i = number of anaesthetised animals in each group.

II — Acute toxicity studies :

They were performed on toads after the manner outlined for anaesthetic activity studies. Animals were observed for the appearance of toxic manifestations, and the recording of number of deaths in 24 hours among each group. Post-mortem examination was done to determine the possible cause of death.

Results were then tabulated to deduce the median lethal dose (LD50) using the Spearman-Karber method (Rossi, 1956) with the original formula :

$$\text{Log LD50} = X_k + \frac{1}{2} d - \frac{d \sum r_i}{n}, \text{ where}$$

X_k = Log dose causing 100% mortality.

d = Log interval of doses.

$\sum r_i$ = Sum of dead animals of each group.

n = Number of animals in each group.

III — Therapeutic Index :

The safety margin of Enflurane in toads was obtained from the ratio of LD50 to AD50 denoting the therapeutic index.

RESULTS

I — Results of anaesthetic activity studies :

Table (1) Shows the details of the minimal effective and maximal tolerated doses of Enflurane and the AD50 with its fiducial limits.

TABLE (1) :

Anaesthetic activity of enflurane in toads

Log. Dose	Dose (g/100 gm)	Number of anaesthesia(r) among groups of toads(n)	Notes
2.00	100.00	0/6	
2.10	125.84	0/6	
2.20	158.49	0/6	
2.30	199.53	0/6	
2.40	251.19	1/6	←minimal effective dose
2.50	316.23	2/6	↑
2.60	398.11	1/6	range of anaesthetic
2.70	501.19	4/6	activity
2.80	630.96	3/6	↓
2.90	794.33	5/6	←maximal tolerated dose
3.00	1000.00	6/6	
3.10	1258.90	6/6	

— AD50 = 402.1 g/100 gm

— 95% fiducial limits
 i — Lower limit = 399.694 g/100 gm
 ii — Upper limit = 405.054 g/100gm

The features of anaesthetic activity of Enflurane in toads were :

1. The mean induction times of anaesthesia were 15 and 3 minutes for the minimal and maximal anaesthetic doses respectively.

2. With minimal effective doses, most toads responded sluggishly to painful stimuli and retained a fair degree of skeletal muscle tone. With maximal anaesthetic doses (AD100), all animals lost response to painful stimuli with nearly complete muscle relaxation.

3. The mean durations of anaesthesia were 2 and 60 minutes for minimal and maximal anaesthetic doses respectively.

4. Mean durations of recovery were 1 and 12 minutes for minimal and maximal doses respectively.

5. No post-anaesthetic sequelae were noted.

II — **Results** of acute toxicity studies :

Table (2) : shows details of minimal lethal dose (MLD), maximal lethal dose (LD100) and median lethal dose (LD50) with its fiducial limits.

The features of enflurane toxicity in toads were :

1. Immediately following the intraperitoneal injection of (MLD), animals went into deep coma which persisted for an average duration of one hour. This was followed by either death or by partial recovery of the animal. In cases ending by death, feeble cardiac contractions persisted for few minutes after cossation of respiration denoting that death was due primarily to respiratory failure.

2. Post-mortem examination of dead animals showed no evidence of local irritation or damage of tissues at the site of injection and no pathological changes in brains, hearts, lungs, livers or kidneys.

TABLE (2) :

Acute toxicity of Enflurane in toads

Log. Dose	**Dose (g/100 gm)**	**No of deaths(r) within 24 hrs among groups of toads(n)**	**Notes**
2.70	501.19	0/6	
2.80	630.96	0/6	
2.90	794.33	0/6	
3.00	1000.00	0/6	
3.10	1228.90	**2/6**	←minimal lethal dose
3.20	1584.90	3/6	toxic range
3.30	1995.30	6/6	←maximal lethal dose
3.40	2511.90	6/6	
3.50	3162.00	6/6	

— LD50 = 1468 g/100 gm

— 95% fiducial limits
- i. Lower limit = 1464.99 g/100 gm
- ii. Upper limit = 1471.33 g/100 gm

III — Therapeutic index of Enflurane in toads :

The therapeutic index of Enflurane in toads was 3.65 (table 3) denoting a wide safety margin.

TABLE (3) :

Therapeutic index of enflurane in toads

Median Value (g/100 gm)	**Species used (toads)**
LD50	1468.0
AD50	402.1
Therapeutic ratio =	
$\frac{LD50}{AD50}$	$\frac{1468.0}{402.1} = 3.65$
** Safety margin	wide

DISCUSSION

By studying the anaesthetic activity and acute toxicity of Enflurane in toads, the present work has demonstrated that the drug possesses a wide safety margin. This confirms the data on dogs given by virtue et al (1966).

Post-mortem examination of toads receiving acute toxic doses of Enflurane showed no evidence of pathological changes in vital organs. Byles et al (1971) reported absence of gross pathological abnormalities in kidneys and livers of dogs and monkeys following the first exposure of those animals to Enflurane at 2MAC. Furthermore, Gasparetto et al (1973), Studying the effect of chronic exposure of rats to Enflurane, found no significant histological changes in brains, lungs, kidneys or genital glands. They

reported slight hyperplasia of the reticulo-endothelial system of the heart and congestion of the red pulp of the spleen.

If the results of animal studies can be transferred to man, the wide safety margin of Enflurane, and the absence of toxic effects on vital organs in toads, obtained in the present study, can give a favourable impression about the safe use of this anaesthetic in humans. But so far the studies showing possible toxic effects of Enflurane in man especially after repeated exposure are not enough to clear Enflurane of such effects. If safety in this respect is proved, Enflurane may be a useful addition to the art of painless surgery.

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BIOCHEMICAL STUDIES OF THE EFFECTS OF MEPIVACAINE (CARBOCAINE) IN RATS

PART (I) :
EFFECT ON SERUM AND MUSCLE ENZYMES

By

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SUMMARY :

A study was carried out on 75 rats divided into 5 equal groups. Rats of 4 groups were I.M. injected with mepivacaine (3 mg/100gm body wt.). Rats of one group were periodically sacrificed at 30 minutes intervals. Rats of the fifth group, acting as control, were injected with saline. The results showed that significant enzymatic changes in serum and muscles followed mepivacaine injection. It was recommended that mepivacaine should be used cautiously in patients with impaired liver function.

INTRODUCTION

The study of the metabolic status following drug administration is an established tool for drug evaluation.

Local anaesthetic drugs, being metabolised in the liver, can produce liver damage including a number of instances of massive hepatic nercosis due to the concomittant hypotension and tissue anoxia that it may produce (innek, 1964).

Mepivacaine is a local anaesthetic, chemically a synthetic amide, which was prepared by Dhuner et al. (1956) and first used clinically by Ekenstam (1956). Concentrations of 0.5-2% give regional analgesia for 2-2.5 hours in man (Collins, 1976).

The present work is carried out to study the effects of mepivacaine on the liver and skeletal muscles of experimental rats which can be achieved biochemically by the determination of both serum and muscle enzymatic activities.

MATERIAL and METHODS

The study was carried out on 75 rats, divided into 5 groups, each including 15 rats. Rats of the first 4 groups were injected with mepivacaine (3 mg/100 gm body weight) in the quadriceps muscles. One group of rats was sacrificed periodically at 30 minutes intervals from the time of injection. Rats of the fifth group were injected with saline to serve as control.

Blood samples were collected by cutting through the juglar path and clear sera were seperated and stored frozen.

After sacrificing the rats, the right pre-injected quadriceps muscles were dissected out, weighed and immersed in fixed volume (10 ml) of saline solution, then transfered to an electric cooled homogenizer. After homogenization, the homogenate was centrifuged and the clear supernaetnt fluid was collected and stored frozen.

Cholinestrase activity in serum and muscle homogenate was determined using the method of Bigg et al. (1953). Serum and muscle glutamic oxalacetic (SGOT and MGOT) and pyruvic transaminase (SGPT and MGPT) activities were determined according to the method of Ritman and Frankel (1957).

Obtained results were analysed statistically using Student's «t» test according to Snedecor (1956).

RESULTS

The obtained results were summarized in table (1).

TABLE (1) :

Means (±S.E.) of serum and muscle enzymatic levels in control and mepivacaine injected groups of rats (15 rats each).

Enzyme	Control group	Group I 30 min.	Group II 60 min.	Group III 90 min.	Group IV 120 min.
S.Ch.E. (I.u./ml)	1.67 ±0.091	1.46 ±0.12	1.41* ±0.08	1.23*** ±0.09	1.65 ±0.09
S.G.O.T. (I.u./L)	36.6 ±1.58	46.8** ±3.12	53.1*** ±1.89	49.6*** ±2.45	37.7 ±1.43
S.G.P.T. (I.u./L)	25.4 ±1.24	26.9 ±1.44	32.9*** ±1.05	28.2 ±1.11	23.1 ±0.75
M.Ch.E. (I.u./gm)	18.6 ±0.57	18.1 ±0.41	18.1 ±0.30	18.1 ±0.25	17.9 ±0.33
M.G.O.T. (u mole/min./gm)	2.0 ±0.06	2.13 ±0.07	1.98* ±0.10	1.59*** ±0.07	1.39*** ±0.05
M.G.P.T. (u mole/min./gm)	1.58 ±0.06	1.47 ±0.07	1.21*** ±0.09	1.05*** ±0.09	0.83*** ±0.06

* Significant ($P < 0.05$)
** Highly significant ($P < 0.01$)
*** Very highly significant ($P < 0.001$)

DISCUSSION

Serum cholinestrase levels in rats injected with mepivacaine, in the present study, showed significant decreases after 60 and 90 minutes from injection compared to rats in the control group. These findings are in agreement with Ferraro et al (1972) who demonstrated that serum cholinestrase activity was decreased following local anaesthetics. As parenchymatous liver cells synthesise serum cholinestrase, Adderhalden (1961) stated that changes in cholinestrase activity could serve as an index of liver function, even in the presence of other normal liver function tests.

Muscle cholinestrase levels in rats injected with mepivacaine, in the present study, showed no change from the control. Libelius et al (1970), using histo-chemical techniques, found that muscle cholinestrase was not affected in rats following bupivacaine which is similar to mepivacaine in that both are pipecolic acid derivatives of xylidide.

Kristerson et al (1965) reported that the highest accumulation of mepivacaine was in the liver and its degradation products were observed 20 minutes after injection. From this point, the decrease of serum cholinestrase activity might be a result of variation in the permeability of the liver cell membrane, either due to accumulation of mepivacaine or its metabolites. This explains the finding in the present study that serum cholinestrase level returned to the normal range after 120 minutes from the injection of rats with mepivacaine. This again coincides with the clinical duration of analgesic action of the drug (Collins, 1976).

The present study demonstrated increases in SGOT and SGPT in rats after injection of mepivacaine. Two explanations can be suggested for this finding, on the one hand, liver cell membrane permeability may be increased due to mepivacaine itself or due to shrinkage of hepatic vasculature with hypoxia resulting in oozing of the protein material including enzymes (Minnek, 1964). On the other hand, muscle trauma at the site of injection may lead to rapid destruction of muscle fibres with leakage of enzymes of the necrotic tissues from areas with intact vasculature at the periphery of the lesion (Daniel et al, 1970). The present study showed significant decreases in MGOT and MGPT after mepivacaine injection.

If the findings obtained in the present work can be applied to man, it may be recommended that mepivacaine should be used cautiously in patients with impaired liver function.

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BIOCHEMICAL STUDIES OF THE EFFECTS OF MEPIVACAINE (CARBOCAINE) IN RATS

PART II :

EFFECT ON PROTEINS, UREA, URIC ACID AND CREATININE

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SUMMARY

A study was carried out on 75 rats divided into 5 equal groups. Mepivacaine (carbocaine) was injected I.M. (3 mg/100 gm body wt) in rats of 4 groups and rats of one group were sacrificed every 30 minutes. Rats of the fifth group were injected with saline and acted as control. The results showed an increase in serum total proteins mostly due to globulin fraction, an increase in serum urea and creatinine levels and a decrease in muscle urea and uric acid. It was concluded that the possibility of subclinical renal toxicity due to mepivacaine, should be born in mind when this drug is administered to patients with bad renal function.

INTRODUCTION

Local anaesthetic agents are peculiar in that they are usually applied to the specific sites where they are to exert their primary pharmacological actions. However, these agents are absorbed systemically and can affect organs other than peripheral nerves. The cardio-vascular system, the liver, the muscles and the kidneys are susceptible to the action of local anaesthetics (Goldenthal, 1968). The requirements for regional anaesthesia with mepivacaine vary considerably, depending on the condition of the patient, and the surgical procedure.

The present work aims to study the effect of mepivacaine on serum and muscle urea and uric acid and serum proteins and creatinine to clarify some possible side-effects of the drug.

MATERIAL and METHODS

The procedure of grouping 75 rats into 5 equal groups and the I.M. injection of mepivacaine (3 mg/100 gm body wt.) to rats of 4 groups and of saline in rats of the fifth control group, together with the collection of samples from serum and muscle homogenate was similar to procedure in Part I of this paper.

Serum total proteins were determined using Biuret method (Wooton, 1964). Serum protein fractions were estimated by simple agar electrophoresis as described by El-Hawary and Ibrahim (1968). Urea was determined in serum and muscles by using the method of Brown (1945). Serum creatinine was estimated by the method described by wooton (1964).

RESULTS

The results obtained for the different studied items were given in tables I and II.

TABLE (1) : Serum proteins (mean±S.E.) in control and mepivacaine injected rats

	Control group	Group I (30 min.)	Group II (60 min.)	Group III (90 min.)	Group IV (120 min.)
Total proteins (gm%)	7.04 ±0.10	7.20 ±0.13	7.53*** ±0.10	7.59*** ±0.10	7.76*** ±0.09
Albumin (gm%)	3.05 ±0.07	3.14 ±0.11	3.31 ±0.09	3.03 ±0.10	3.08 ±0.07
Alpha-globulin (gm%)	1.33 ±0.03	1.35 ±0.03	1.39 ±0.02	1.59*** ±0.04	1.41** ±0.02
Beta-globulin (gm%)	1.59 ±0.04	1.62 ±0.03	1.66* ±0.05	1.73** ±0.04	1.93*** ±0.02
Gamma-globulin (gm%)	1.07 ±0.03	1.09 ±0.03	1.16* ±0.03	1.24*** ±0.03	1.34*** ±0.02
Total Globulins (gm%)	3.99 ±0.06	4.06 ±0.06	4.22** ±0.06	4.56*** ±0.08	4.68*** ±0.04

* Significant (P < 0.05)
** Highly significant (P < 0.01)
*** Very highly significant (P < 0.001)

TABLE (II) : Serum and muscle non-protein nitrogen (mean ± S.E.) in control and mepivacaine injected rats

	Control group	Group I (30 min.)	Group II (60 min.)	Group III (90 min.)	Group IV (120 min.)
Serum urea (mg %)	22.88 ±0.64	27.58*** ±0.73	34.37*** ±0.91	28,95*** ±0.67	25.00** ±0.48
Serum uric Acid (mg %)	7.76 ±0.27	4.45 ±0.48	4.23 ±0.44	4.24 ±0.26	4.57 ±0.37
Serum creatinine (mg %)	1.76 ±0.11	1.71 ±0.08	1.80 ±0.07	1.92 ±0.12	2.29*** ±0.12
Muscle urea (mg %)	1.27 ±0.07	0.8*** ±0.06	0.51*** ±0.06	0.63*** ±0.04	0.61*** ±0.04
Muscle uric acid (mg %)	0.38 ±0.04	0.37 ±0.02	0.36 ±0.01	0.21*** ±0.01	0.26** ±0.02

* Significant (P < 0.05)
** Highly Significant (P <0.01)
*** Very highly significant (P < 0.001)

DISCUSSION

The present work has revealed a significant increase in serum total proteins after one hour from the I.M. injection of mepivacaine in the experimental rats. This increase was mostly due to significant increase in globulin fractions. Tevyakov (1960), found that novocaine administration in rabbits caused increased serum protein levels. Bushkov and Danilov (1964), observed an increase in serum total proteins following local anaesthetics, indicating mobilization of the protective reactions of the organism. Increased globulins after mepivacaine might be also due to tissue damage as a result of mechanical injury induced by injection, or due to the destructive effect of the drug or its metabolites on the rat muscles (Benoit and Belt, 1970).

The present study has demonstrated significant increase in serum urea and creatinine following mepivacaine injection in rats. This might be due to an increase in the renal vascular resistance with a reduction in the effective renal plasma flow resulting from arterial hypotension by the drug. Hetricle et al (1973), reported that the observed subclinical renal toxicity was indicated by elevated levels of serum urea and creatinine concentrations.

A significant decrease of muscle urea and uric acid followed mepivacaine injection in rats. Grey and Geddes (1954), mentioned that local anaesthetics block the enzymatic chain involved in the intracellular respiration at the cytochrome-C-cytochrome oxidase level which account for the decrease of ATP formation and the inhibition of urea synthesis. Mepivacaine or its metabolites might have a direct inhibitory effect on the enzyme systems involved in uric acid synthesis including guanase, adenase or xanthine oxidase.

It might be concluded that the possibility of subclinical renal toxicity due to mepivacaine, should be born in mind whenever this drug is administered to patients with bad renal functions.

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HAEMATOLOGICAL, BIOCHEMICAL AND HISTOPATHOLOGICAL STUDIES OF THIOPENTONE IN THE EXPERIMENTAL DOG.

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SUMMARY

Haematological, biochemical and histopathological studies are carried out on 30 dogs anaesthetized by thiopentone administered intraperitoneally. They were divided into a control group and a study group, each including 15 dogs.

In the blood, thiopentone induced leucocytosis with neutrophilia and lymphopenia. It decreased potassium, protein and increased glucose levels. In the CSF, thiopentone decreased mature neuthrophils, and increased small lymphocytes. It decreased sodium and chloride levels and increased glucose level. Histopathologically, one single injection caused congestion of the liver and lung. While repeated injections led to their infiltration with round cells. Possible explanation concerning the different changes are suggested and discussed.

INTRODUCTION

Smith et al (1948) experimenting on the cat and Graca and Grasts (1957) experimenting on the dog, reported that thiopentone induces an immediate decrease in peripheral leucocytic count predominantly neutrophils with an increase in lymphocytes which reverses upon awakening from anaesthesia. In normal and splenectomized dogs after thiopentone anaesthesia, Usenik and Chronkite (1965) noted that the leucocytic count decreases with no significant changes in the differential count.

A fall in serum potassium level during thiopentone anaesthesia was reported by Stevenson (1960) in the experimental dog and by other authors (List. 1967 and Bali and Dundee, 1974) in man.

A mild hyperglycaemic effect has been observed in the dog during thiopentone anaesthesia (Booker, 1946 ; Booker et al, 1949 ; Booker et al, 1952).

Thiopentone was shown to decrease plasma proteins in the experimental sheep (O'Brien and Heath, 1968) and in man (Bond and Parson, 1970 ; Albert, 1971 and Magora et al, 1974).

Cerebro-spinal fluid (CSF) in derived from the blood plasma and therefore has qualitatively, the same composition. However, the discrepencies shown to exist between the ionic concentrations in the CSF and the concentration of the same substances in blood plasma dialysate indicate that the fluid is not a simple filtrate but rather a product of an active selective secretory mechanism (Sweet et al., 1954).

The effect of anaesthesia in general and thiopentone in particular on CSF constituents are poorly considered in as much literature is concerned.

The present work was designed to fulfil a comprehensive study concerning haematological, biochemical and histopathological effects of thiopentone anaesthesia administered intraperitoneally in the experimnetal dog.

MATERIAL and METHODS

Material :

Thirty healthy dogs of a mean weight of 15 kg. were used. They were divided into 2 groups each of 15. The first group was used as control. The second group was injected intraperitoneally with thiopentone sodium in a dose of 10 mg/Kg.B.Wt.

Methods :

A. Blood

1. Haematological investigations :

Two mls of blood were collected from the tibial vein on EDTA and examined for total blood count (Wintrobe, 1967), haemoglobin content (cyanmethaemoglobin method, lynch et al, 1969), packed cell volume (microhaematocrit method) and the differential leucocyitc count (Schalm et al, 1975).

2. Biochemical examination of the serum :

Serum was examined for sodium, potassium, calcium, magnesium, chlorides, total protein, glucose, urea, creatinine and bilirubin.

B. Cerebro-spinal fluid :

1. Collection of CSF :

The cerebro-spinal fluid was collected from the cisterna magna at the atlanto-occipital articulation in dogs according to the method adopted by McGrath (1956).

2. Physical examination :

The physical properties of CSF including the colour, consistency, turbidity and reaction were investigated. The reaction was determined by Beckman pH-meter.

3. Cytological examination :

The cytological examination was done after the method described by Cornelius and Kaneko (1963).

4. Biochemical investigations :

Biochemical analysis of CSF included :

Sodium and potassium estimation by using flame photometer, calcium and magnesium after Kramer and Tisdall (1921), Chlorides after Whitehorn (1921), total protein after Weichsllaum (1946), glucose after Folin and Wu (1920), urea after Natelson (1957), creatinine after Owen et al (1954) and bilirubin after Malloy and Evelyn (1937).

The biochemical tests used for the serum as well as for the cerebro-spinal fluid were the same.

5. Histopathological examination :

Specimens from liver, kidney, spleen, heart, lung, brain and spinal cord were fixed in normal saline, embedded in paraffin and sections, 3-5 microns thickness, were prepared and stained with haematoxylene and eosine.

The specimens were obtained from dogs with single intraperitoneal and repeated injections of thiopentone for 15 days.

RESULTS

The effect of intraperitoneal injection of thiopentone on the blood picture of dogs (Table 1).

The effect of intraperitoneal injection of thiopentone on some biochemical constituents of the blood of dogs (Table 2).

The effect of intraperitoneal injection of thiopentone on the physical properties of CSF in dogs (Table 3).

The effect of intraperitoneal injection of thiopentone on the cell count of CSF in dogs (Table 4).

The effect of intraperitoneal injection of thiopentone on some biochemical constituents of CSF in dogs (Table 5).

TABLE (1) :

Effect of intraperitoneal injection of thiopentone on the blood picture of dogs.

Haematological tests	Control 15 dogs (mean ± S.E.)	Anaesthetised 15 dogs (mean ± S.E.)
Haemoglobin (g/dL)	13.64±1.85	12.79±1.44
R.B.Cs (10 6/uL)	6.45±1.34	5.86±0.97
P.C.V. (%)	44.50±2.56	40.55±2.35
W.B.Cs. (1000/uL)	9347±654	11259±473**
Neutrophils (%)	58.15±0.46	46.17±0.63***
Lymphocytes (%)	32.32±0.82	45.26±0.44***
Monocytes (%)	4.24±0.15	4.37±0.25
Eosinophils (%)	5.28±0.33	5.19±0.39

S.E. = Standard error
** = $P < 0.01$ *** = $P < 0.001$

TABLE (2) :

Effect of intraperitoneal injection of thiopentone on some biochemical constituents in the blood of dogs.

Biochemical constituents	Control 15 dogs (mean±S.E.)	Anaesthetised 15 dogs (mean±S.E.)
	Inorganic constituents	
Sodium (mg%)	431.25±79.46	445.17±81.52
Potassium (mg%)	22.73± 1.86	18.36± 0.64*
Calcium (mg%)	11.64± 1.35	10.97± 1.56
Magnesium (mg%)	2.79± 0.32	2.37± 0.26
Chlorides (mg%)	412.28±68.51	408.54±81.33
	Organic constituents	
Total protein (gm%)	6.78± 0.15	6.04± 0.19**
Glucose (mg%)	71.47± 1.68	84.77± 2.39**
Urea (mg%)	27.35± 1.23	25.89± 1.48
Creatinine (mg%)	1.15± 0.12	1.10± 0.11
Bilirubin (mg%)	0.01± 0.002	0.01± 0.004

S.E. = Standard error
* = $P < 0.05$ ** = $P < 0.01$

TABLE (3):

The effect of intraperitoneal injection of thiopentone on the physical properties of CSF in dogs

Physical properties	Control 15 dogs (mean±S.E.)	Anaesthetised 15 dogs (mean±S.E.)
Colour	colourless	colourless
Aspect	clear	clear
Clot	absent	absent
PH	7.45±0.21	7.55±0.35

S.E. = Standard error

TABLE (4):

The effect of intraperitoneal injection of thiopentone on the cell count of CSF in dogs

Types of cells (%)	Control 15 dogs (mean±S.E.)	Anaesthetised 15 dogs (mean±S.E.)
Mature neutrophils	2.94±0.23	1.56±0.34*
Immature neutrophils	5.87±1.49	3.69±1.77
Small lymphocytes	60.74±1.67	65.95±1.33*
Large lymphocytes	16.68±1.44	18.18±1.46
Degenerated lymphocytes	13.88±1.21	10.52±1.34

S.E. = Standard error
* = $P < 0.05$

TABLE (5) :

The effect of intraperitoneal injection of thiopentone on some biochemical constituents of CSF in dogs

Biochemical constituents	**Control 15 dogs (mean±S.E.)**	**Anaesthetised 15 dogs (mean±S.E.)**
	Inorganic constituents	
Sodium (mEq/L)	152.77±0.14	151.08±0.21*
Potassium (mEq/L)	3.20±0.01	3.19±0.01
Calcium (mEq/L)	3.28±0.05	3.32±0.07
Magnesium (mEq/L)	2.23±0.03	2.18±0.12
Chlorides (mEq/L)	132.69±0.44	130.70±0.38**
	Organic constituents	
Total protein (gm%)	23.52±0.33	28.54±0.35
Glucose (mg%)	68.25±0.69	74.35±0.58**
Urea (mg%)	7.86±0.14	7.21±0.47
Creatinine (mg%)	0.41±0.06	0.42±0.09
Bilirubin (mg%)	0.003±0.0001	0.004±0.0003

S.E. = Standard error
* = $P < 0.05$ ** = $P < 0.01$

Histopathological picture :

In one single dose of intraperitoneal injection of thiopentone, there was only slight congestion of the liver confined to the distention of the central vein with red blood corpuscles. The lung showed active hyperaemia.

Repeated intraperitoneal injections of thiopentone for 15 days showed the following :

The liver was severely congested, the central veins and sinusoids were dilated and packed with red cells, infiltration of round cells was found in the Glisson's capsules with degenerative changes in the hepatic cells. (Fig. 1). The lung showed dilatation

of the perialveolar and peribronchial blood vessels. Some of the alveolar spaces were widened and distorted. There was infiltration of large amounts of round cells in the interalveolar septa (Fig. 2).

Fig. 1 : Liver of dog after repeated intraperitoneal injection with thiopentone Showing congestion and infiltration with round cells (X 200, Stain H and E.)

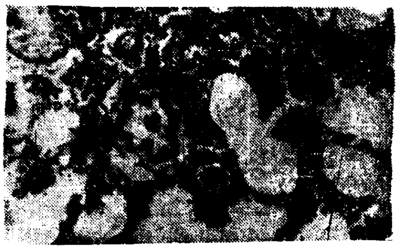

Fig. 2 : Lung of dog after repeated intraperitoneal injection with thiopentone showing congestion and infiltration with large amounts of round cells in the interalveolar septa, (X 200, Stain H and E.).

DISCUSSION

In the present work there is a decrease in neutrophils and an increase in lymphocytes after intraperitoneal injection of thiopentone in dogs. These effects are in agreement with Smith et al (1948) and Graca and Grasts (1957). There is leucocytosis which is not in agreement with Usenik and Chronkite (1965). This discrepensy may be due to the difference in the rote of injection and the

iritation of the drug, because Usenik and Chronkite (1965) used the intravenous route while we used the intraperitoneal one.

The present work shows a significant decrease in the serum potassium after intraperitoneal injection of thiopentone in the dog. The decrease in serum potassium was in agreement with Stevenson (1960) ; List (1967) and Bali and Dundee (1974). This may be due to a metabolic factor causing the potassium to enter the cell leading to its decrease in the serum (List 1967).

The present work shows a significant increase in the blood sugar level after intraperitoneal injection of thiopentone in dogs. This findings is in agreement with Booker (1946) ; Booker et al (1949) and Booker et al (1952).

The present work demonstrates a significant decrease in plasma proteins during thiopentone anaesthesia in dogs, in aggreement with O'Brien and Heath (1968). This was attributed by Albert (1971) to a direct sympathatic stimulation causing vasodilatation and movement of fluids from extra to intra vascular space, resulting in haemodilution.

Concerning the cerebro-spinal fluid, the intraperitoneal injection of thiopentone has no effect on its physical properties, but has an effect on the cell count where there was a significant decrease in the mature neutrophils and increase in the small lymphocytes.

The present work shows a significant decrease in the sodium and chloride contents in the CSF during intraperitoneal injection of thiopentone anaesthesia. The fact that the sodium and chloride concentrations in cerebro-spinal fluid are greater than those of the plasma suggests the presence of an active secretory mechanism for these substances into the CSF (Davson 1967). The decrease in sodium and chlorides in CSF during anaesthesia might be due to thiopentone inhibiting their active transfer mechanism from plasma to cerebro-spinal fluid. an explanation previously suggested by Kaneko and Cornelius (1971). The decrease in chloride after the intraperitoneal administration of thiopentone correlates with the decrease of this element in case of protracted vomiting and minigitis in dogs (Coles. 1974).

There was a significant increase in the glucose level in CSF after intraperitoneal injection of thiopentone in dogs. It was reported by Cornelius and Kaneko (1963) and Davson (1967) that the concentration of glucose in CSF approximates 60 to 70% of the blood glucose level. The glucose in CSF is dependent upon the blood glucose level. selective permeability of the blood-cerebrospinal fluid barrier and the presence or absence of strong glycolytic activity (Davson, 1967 ; Kaneko and Cornelius, 1971 and Medway et al, 1973). An increased glucose level (hyperglycorrhachia) during thiopentone injection suggests that this drug enhances the transport of glucose across the blood-brain barrier.

The insignificant changes in creatinine, bilirubin and urea concentration after intraperitoneal injection of thiopentone may be attributed to the difficulty of their penetration through the blood-cerebrospinal fluid barrier due to their larger molecules when compared with those of the electrolytes and sugar (Davson, 1967, Levinson and Macfate, 1969).

Concerning the histopathological changes, congestion of the liver after single thiopentone injection may be the result of detoxication of thiopentone in the hepatic cells (Shideman et al, 1949 ; and Richards 1941). In the repeated intraperitoneal injection of thiopentone there was a round cell infiltration in the liver and lung, that may be due to the cumulative effect of thiopentone (Collins and Vincent 1976).

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EFFECT OF HYPOXIA, HYPERCARBIA, HYPERVENTILATION AND JUGLAR COMPRESSION ON INCREASED INTRACRANIAL PRESSURE

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SUMMARY

A study has been carried out on 12 dogs to find out the effects of hypoxia, hypercarbia, hyperventilation and juglar venous compression on intracranial pressure when it is already high. I.C.P. was incread artificially by inflating a small balloon inside the parietal temporal region. Gradually increasing the size of the balloon mass, was followed by gradual increases in the ICP, till vital centres were affected. The study was carried out in this stage. Hyperventilation reduced I.C.P. rapidly then I.C.P rose gradullay. Juglar vein compression was shown to be more hazardous in raising I.C.P. than hypoxia or hypercarbia.

INTRODUCTION

Intra-cranial pressure (I.C.P.) reading presents the summation of different factors, mainly, systemic blood pressure, peripheral vascular resistance of the brain, gas tensions in the arterial

blood, venous pressure, rate of C.S.F. secretion and absorption, respiratory movement as well as skull and brain volume and elasticity (Lundberg, 1960 and Laugfitt, 1964).

Control of brain oedema by hyperventilation during surgery is an accepted technique. Some investigators believe that prolonged hyperventilation may cause cellular hypoxia (Lundberg, 1959). That venous engorgement increase the intra-cranial pressure is a constant observation of all surgeons.

The response of I.C.P. to hyperventilation with oxygen, hypercapnia and increased venous pressure is more marked in cases with increased I.C.P. in both directions, whether a rise or a fall, provided that the I.C.P. does not reach the point of collapsing the veins and seriously hindering the arterial perfusion, that is to say, putting the brain autoregulation out of action.

The response of I.C.P. to rapidly expanding mass lesion was studied by Laugfitt (1964), who demonstrated a gradual rise of I.C.P. corresponding to the size of the mass till it reaches the decompensating point where the changes take a notorious cerscendo curve.

This study is carried out to find out the relation during anaesthesia between hypoxia, hyperventilation, hypercapnia and obstruction of venous return and the I.C.P. in dogs with already increased I.C.P.

MATERIAL and METHODS

This study included 12 dogs of 20 Kg average weight. Induction of anaesthesia was achieved by I.V. thiopentone sodium in a mean dose of 20 mg/kg, followed by succinyl-choline and tracheal intubation under direct vision laryngoscopy. The airway was attached to a Boyle's apparatus giving an oxygen flow of 4 L/min. Supplementation by small doses of I.V. thiopentone sodium was needed in two dogs out of twelve. The dog was then turned to the lateral position. Parietal burr-holing was performed on the already shaved scalp. The dura was opened and a small balloon

was introduced in the parietal lobe, filled with saline and connected to a water manometer. I.C.P. was measured with gradual inflation of the balloon by gradually increasing volumes of saline till the dog showed respiratory irregularity or cardiac arrhythmias as a sign of alteration of the vital centres. Mogs were categorised to a plan into 2 groups :

I — Six dogs were then subjected to hypoventilation by giving minute volumes of 2 L/min of oxygen for 15 minutes, followed by 1 L/min. for further 15 minutes and I.C.P. was measured every 5 minutes. The dogs were then allowed back on 4 L/min of oxygen till the I.C.P. returned to its level before testing hypoventilation. Hyperventilation effect on I.C.P. was then tested using 8 L/min. of oxygen and controlled respiration, and I.C.P. measurements were recorded every 5 min. for 15 min.

II — The other six dogs were subjected to inhalation of 5% Co_2 mixture with air and I.C.P. was measured every 5 min for 15 min. After I.C.P. returned to its pre-level by inhaling oxygen, the effect of venous engorgement was tested. Digital compression of both juglar veins was performed for further 10 min., allowing intervals for the dogs to recover whenever the I.C.P. was measured.

RESULTS

Table (1) shows the effect of gradually inflating the balloon by 1—8 ml of saline during which signs of alteration of vital functions appeared.

Table (2) shows the effect of hypoventilation and hyperventilation on an already raised I.C.P. in six dogs.

Table (3) : shows the effect of inhalation of 5% Co_2 mixture in air and the effect of juglar compression on raised I.C.P. in the other six dogs.

TABLE (I) : Effect of the size of the balloon mass on I.C.P. (mmH_2O) in dogs.

Dogs	Control Balloon Size							
	1 ml	2 ml	3 ml	4 ml	5 ml	6 ml	7 ml	8 ml
1	60	72	95	100	150	170	200	290 *
2	78	79	90	105	140	210	300	455 *
3	72	84	100	120	160	240	310	390 *
4	64	75	100	130	180	210	340	400 *
5	89	110	140	170	200	250	300	360 *
6	90	110	135	180	205	260	370	410 *
7	73	94	120	150	195	240	290	340 *
8	67	78	98	130	160	190	220	295 *
9	83	98	105	140	170	200	250	320 *
10	81	100	110	160	195	220	310	360 *
11	76	95	120	170	210	240	310	378 *
12	70	90	130	165	190	200	270	340 *
Σ	903	1085	1333	1720	2155	2630	3470	<1338
×	75.25	90.42	111.08	143.33	179.58	219.17	289.17	361.5
t		2.3155	6.0799	8.2221	16.92	17.194	15.0119	14.1907
p		<0.05	<.001	<.001	<.001	<0.001	<.001	<0.001

* alteration of vital centeres

TABLE (II) :

Effect of hypo- and Hyperventilation on I.C.P. (mmH_2O) in dogs.

Dog.	Control I.C.P.	Hypoventilation						Hyperventilation		
		2 L/min.			1 L/min.					
	(mmH_2O)	5 min.	10 min.	15 min.	5 min.	10 min.	15 min.	5 min.	10 min.	15 min.
1	290	300	305	305	320	340	370	160	180	210
2	455	455	460	460	480	500	500	290	300	340
3	390	400	405	405	440	460	460	210	240	250
4	400	420	430	430	450	465	480	205	240	260
5	360	360	360	365	365	380	390	130	150	165
6	410	415	420	420	420	420	430	160	180	190
Σ	2305	2350	2380	2385	2475	2565	2630	1155	1290	2415
Mean	384.1	391.67	396.67	397.5	412.5	427.5	438.33	192.5	215	402.5
t		0.0129	0.0310	0.0805	0.0926	1.8468	1.9002	6.2419	3.6276	0.1609
P		>0.05	>0.05	>0.05	>0.05	>0.05	>0.05	<0.001	<0.01	≥ 0.05

TABLE (III) :

Effect of carbon dioxide inhalation and juglar Compression
on I.C.P. (mmH_2O) in dogs

Dog	Control I.C.P. (mmH_2O)	Carbon dioxide inhalation			Jugular vein compression	
		5 min	10 min.	15 min.	5 min.	10 min.
1	340	345	360	370	500	550
2	295	320	350	400	550	700
3	320	355	370	385	640	780
4	360	370	359	420	735	820
5	378	400	405	310	620	760
6	340	365	380	395	810	900
Σ	2033	2155	2224	2380	3855	4510
$\times$	338.83	359,19	370,67	396.67	642.5	751.67
t		0.09561	0.0914	0.3314	5.8699	6.7001
Sig		>0.05	>0.05	>0.05	<0.001	<0.001

DISCUSSION

The present study has preferred to use the intra-cerebral balloon in monitoring I.C.P. for various reasons. The subarachroid CSF pressure reflects the changes in I.C.P., but not the actual pressure the brain tissue is subjected to. The ventricles are liable to collapse with unilateral expanding mass lesion, due to the pressure gradient and the brain tissue elasticity. This method has been used in the present study due to absence of other methods within hand.

The present work has shown that significant increases in I.C.P. took place with gradual inflation of the balloon. The response shows slow initial rise followed by a rapid crescendo rise, in agreement with Laugfitt (1964).

Hypoventilation has induced rises of I.C.P. which are not statistically significant over about 30 minutes. This may be explained by the low oxygen requirements of the dog and its further reduction by the lowered consumption rates under anaesthesia.

Hyperventilation produced significant rapid fall in I.C.P. within the first five minutes of its application followed by gradual rise within the next ten minutes. Rapid fall may be explained on the basis of vasoconstriction of cerebral blood vessels with reduction of the brain blood content. With prolonged vasoconstriction, subsequent cellular ischaemia and carbon dioxide accumulation may be contributing factors in the occurrence of vasodilatation and increasing the brain blood volume, allowing the gradual rise of the I.C.P. within these 10 minutes. This explanation goes in agreement with Hay (1962), and Tundal (1976).

The carbon dioxide mixture inhalation produced non-significant rise in I.C.P., which amounted to 17% rise. Carbon dioxide is expected to cause vasodilatation and to increase the brain fluid content by altering the permeability of the capillaries. However, such changes are slow to develop and may take time to increase I.C.P. to significant levels (Kindet, 1972).

Juglar compression has been found to affect the I.C.P. to pronounced levels. Unfortunately, it was not feasible to measure the

cranial venous pressure. The rise in I.C.P. after juglar compression was instantaneous. The importance of such information is the fact that kinking of the neck producing juglar venous obstruction may be thought of as being more hazardous in inducing a rise in I.C.P. than hypoxia or hypercapnia. Attempts to lower I.C.P. produced by juglar venous compression, in one of the dogs, failed and hyperventilation produced almost no effect.

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